

Original Article

Clinical efficacy of lower abdominal transcutaneous electrical stimulation combined with mifepristone plus methyl carboprost suppository in the treatment of missed abortion and its effects on endometrial thickness, hemodynamics, serum hypoxia inducible factor 1 α and vascular endothelial growth factor

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Abstract: Objective: To investigate the clinical efficacy of lower abdominal transcutaneous electrical stimulation combined with mifepristone plus methyl carboprost suppository in the treatment of missed abortion and its effects on endometrial thickness, hemodynamics, serum hypoxia inducible factor 1 α (HIF-1 α) and vascular endothelial growth factor (VEGF). Methods: Retrospective analysis of 86 cases of missed abortion patients who were divided according to treatment methods into an observation group (44 cases) and control group (42 cases). The control group was treated with mifepristone plus methyl carboprost suppository, and the observation group was treated with transcutaneous electrical stimulation on the basis of control group. The clinical efficacy, incidence of complications, changes of endometrial thickness, pulsatility index (PI) of hemodynamic index, resistance index (RI), end arterial systolic/diastolic velocity ratio (S/D), and serum HIF-1 α and VEGF levels before and after treatment were compared between the two groups. Results: The amount of vaginal bleeding, bleeding time and menstrual recovery time in the observation group were less than those in the control group ($P < 0.05$). After treatment, the endometrial thickness of the observation group was greater than that of the control group ($P < 0.05$). RI, PI and S/D in the observation group were all lower than those in the control group ($P < 0.05$). The expression levels of serum HIF-1 α and VEGF in the observation group were lower than those before treatment ($P < 0.05$). The negative conversion rate of human chorionic gonadotropin (HCG) in the observation group was higher than that in the control group at 1 and 2 weeks after treatment ($P < 0.05$), and there was no statistical significance in the negative conversion rate of HCG in the two groups at 3 weeks after treatment ($P > 0.05$). The incidence of complications in the observation group was lower than that in the control group ($P < 0.05$). Conclusion: Transcutaneous electric stimulation combined with mifepristone plus methyl carboprost suppository for treatment of missed abortion can shorten the time of vaginal bleeding, reduce the amount of vaginal bleeding and promote the increase of endometrial thickness. The mechanism may be related to improvement of the hemodynamic status of the endometrium and down-regulation of the expression levels of serum HIF-1 α and VEGF.

Keywords: Missed abortion, transcutaneous electrical stimulation, mifepristone, methyl carboprost suppository, endometrial thickness, hemodynamics

Introduction

Missed abortion refers to when the embryo or fetus has died and remains in the uterine cavity without a timely discharge; which is a common disease in obstetrics and the incidence rate is as high as 13.4% [1]. With the implementation of the two-child policy in China, the number of

elderly pregnant women is increasing, and the incidence of missed abortion is increasing [2]. After the occurrence of a missed abortion, the dead fetal tissue is still organized and will adhere to the uterine wall, resulting in increased difficulty in treatment [3]. Mifepristone plus methyl carboprost suppository is one of the common methods for the treatment of a miss-

ed abortion. It has a positive effect on promoting the expulsion of the embryo or dead fetus, but it has many complications, and has little effect on the problems of intrauterine adhesions and menstrual disorders [4-6]. It is difficult for the embryo to clear the uterus because of the artificial luteal fetus protection treatment and the adhesion between the fetal tissue and the uterine wall. In addition, the operation of clearing the uterus inevitably causes damage to the endometrium and the uterine mucosa. Some patients even need to clear the uterus twice or repeatedly, which increases the incidence of complications such as menstrual disorders, periodic lower abdominal pain and pelvic tenderness, and even affects the fertility of patients [7, 8]. Transcutaneous electrical stimulation is based on the principle of neuro-electrophysiology, it uses low-frequency pulsed electrical stimulation of acupuncture points to excite the neuromuscular symptoms and improves microcirculation. Relevant studies have shown that transcutaneous electrical stimulation can promote menstruation recovery in patients with a missed abortion. Cuan et al. [9] have shown that assisted lower abdominal transcutaneous electrical stimulation can significantly improve endometrial thickness increase, promote the recovery of endometrial hemodynamics, reduce the amount of postoperative vaginal bleeding, and prevent complications such as hypomenorrhea in women with missed or incomplete abortion after the operation of clearing the uterus. However, there are few reports on the efficacy of its combination with mifepristone plus methyl carboprost suppository. Therefore, it is inferred that the treatment of missed abortion with transcutaneous electrical stimulation combined with mifepristone plus methyl carboprost suppository can reduce the complications and promote the recovery of the uterus and menstruation. Therefore, this study was done mainly to investigate the clinical effect of transcutaneous electrical stimulation combined with mifepristone plus methyl carboprost suppository in the treatment of missed abortion and its effects on endometrial thickness, hemodynamics and complications, and also to observe the effect of relevant serum indexes hypoxia inducible factor-1 α (HIF-1 α) and vascular endothelial growth factor (VEGF) related to uterine recovery.

Materials and methods

General information

A total of 86 patients with missed abortion who were admitted to our hospital from May 2015 to June 2017 were selected for this research. Inclusion criteria: (1) patients who met the diagnostic criteria for missed abortion in *Chinese Obstetrics and Gynecology* [10]; (2) patients who were aged between 20 and 40 years old; (3) patients who were not allergic to the drugs used in the study; (4) patients with normal electrocardiogram and without coagulation dysfunction. Exclusion criteria: (1) patients with liver and kidney dysfunction; (2) patients who were complicated with serious primary hypertension, diabetes and other medical system diseases; (3) patients with cognitive dysfunction; (4) patients with genital organ inflammation; (5) patients with organic diseases of reproductive organs; (6) patients with incomplete clinical data. According to treatment methods, the patients were divided into an observation group (44 cases) and a control group (42 cases). The study was approved by the Ethics Committee of Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing Maternal and Child Health Care Hospital.

Methods

The control group was treated with mifepristone plus methyl carboprost suppository. Mifepristone (Hubei Gedian Renfu Pharmaceutical Co., Ltd., China, specification: 25 mg/tablet) 25 mg/time, 2 times/d, oral for 3 d. On the 4th d, two methyl carboprost suppositories (Shenyang No.1 Pharmaceutical Co., Ltd. of Northeast Pharmaceutical Group, China) were implanted into the posterior vault of vagina, and the uterus was cleaned 6 h later, and rechecked 3 d later. If there was any residue, the uterus was cleaned again.

The observation group was treated with transcutaneous electrical stimulation on the basis of control group. The neuromuscular stimulation treatment device produced by Guangzhou Shanshan Company (China) was used for treatment, and the electrode sheets were placed at Guanyuan Yu and Guanyuan acupoints. Treatment parameters: current intensity 45-50 mA, frequency 35 Hz, pulse width 200 μ s, treatment time 30 min/d, 1 time/d, continuous treatment for 7 d.

Table 1. Comparison of general information between the two groups ($\bar{x} \pm s, n$)

Group	Average age (Yr)	Menopause time (d)	Times of pregnancy (time)	Gestational weeks (week)	Gestational sac size (cm)	Puerpera	
						Unipara	Multipara
Observation group (n=44)	27.8±5.2	82.4±6.6	2.32±0.85	7.8±2.1	3.05±0.46	34	10
Control group (n=42)	27.2±5.7	80.6±7.2	2.37±0.78	7.9±2.3	3.11±0.58	30	12
χ^2/t	0.510	1.209	0.284	0.211	0.533	0.386	
P	0.611	0.230	0.777	0.834	0.596	0.535	

Evaluation criterion

(1) The treatment of the two groups were observed, including the number of cases of embryo delivery, the time of embryo delivery and the amount of bleeding. (2) Endometrial thickness: at 15 d after treatment, the endometrial thickness was examined by Japanese aloca a5 color Doppler ultrasound. (3) Before treatment and at 15 d after treatment, the uterine artery pulsatility index (PI), resistance index (RI) and end arterial systolic/diastolic velocity ratio (S/D) were examined by Japanese aloca a5 color Doppler ultrasound. (4) Before treatment and at 7 d after treatment, 5 mL of venous blood was collected and centrifuged at 3000 r/min for 10 min, and serum was taken. The levels of serum HIF-1 α (the kit was purchased from R&D Company of the United States) and serum VEGF (the kit was purchased from Shanghai Senxiong Biotechnology Co., Ltd., China) were measured by enzyme-linked immunosorbent assay (ELISA). The operation was carried out in strict accordance with the instructions of the kit. (5) Before and after treatment, 3 mL of venous blood was taken and centrifuged at 3000 r/min for 10 min, and serum was taken. Human chorionic gonadotropin (HCG) was detected by ELISA, and 10 $\mu\text{g/L}$ was regarded as turning negative. The kit was purchased from German TSZ Company, and the operation strictly followed the instructions of the kit. (6) After treatment, complications such as intrauterine adhesions, menstrual disorders and periodic lower abdominal pain in the two groups were observed. The total incidence of complications = the number of complications \div the total number of cases \times 100%.

Statistical analysis

SPSS 25.0 statistical software was used to analyze the data. The measurement data were expressed as $\bar{x} \pm s$, and the enumeration data were expressed as percentage (%). Independen-

dent sample t-test was used for comparison between groups, and paired t-test was used for comparison before and after treatment within groups. There is a significant difference at $P < 0.05$.

Results

No significant difference in general information between the two groups

There was no significant difference in terms of the average age, menopause time, times of pregnancy, gestational weeks, and gestational sac size between the two groups ($P > 0.05$), and they are comparable. See **Table 1**.

The amount of vaginal bleeding, bleeding time, menstrual recovery time and endometrial thickness improved significantly in the observation group

The amount of vaginal bleeding, bleeding time and menstrual recovery time in the observation group were less than those in the control group, and the endometrial thickness in the observation group was greater than that in the control group (both $P < 0.05$). See **Table 2; Figure 1**.

Hemodynamic indexes improved significantly in the observation group

PI, RI and S/D in both groups were lower after treatment than before treatment, and the observation group was lower than the control group ($P < 0.05$). See **Table 3; Figure 2**.

Levels of serum HIF-1 α and VEGF improved significantly in the observation group

After treatment, the levels of serum HIF-1 α and VEGF were lower than those before treatment, and the levels in the observation group were lower than those in the control group, with a significant difference (both $P < 0.05$). See **Table 4; Figure 3**.

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Table 2. Comparison of treatment status and endometrial thickness between the two groups [$\bar{x} \pm s$, n (%)]

Group	Amount of vaginal bleeding (mL)	Bleeding time (d)	Menstrual recovery time (d)	Endometrial thickness (mm)
Observation group (n=44)	20.14±2.85	1.1±0.9	30.1±4.4	6.36±1.67
Control group (n=42)	28.36±2.63	2.7±1.2	35.6±3.6	5.21±1.55
t	13.882	7.016	6.327	3.306
P	0.000	0.000	0.000	0.000

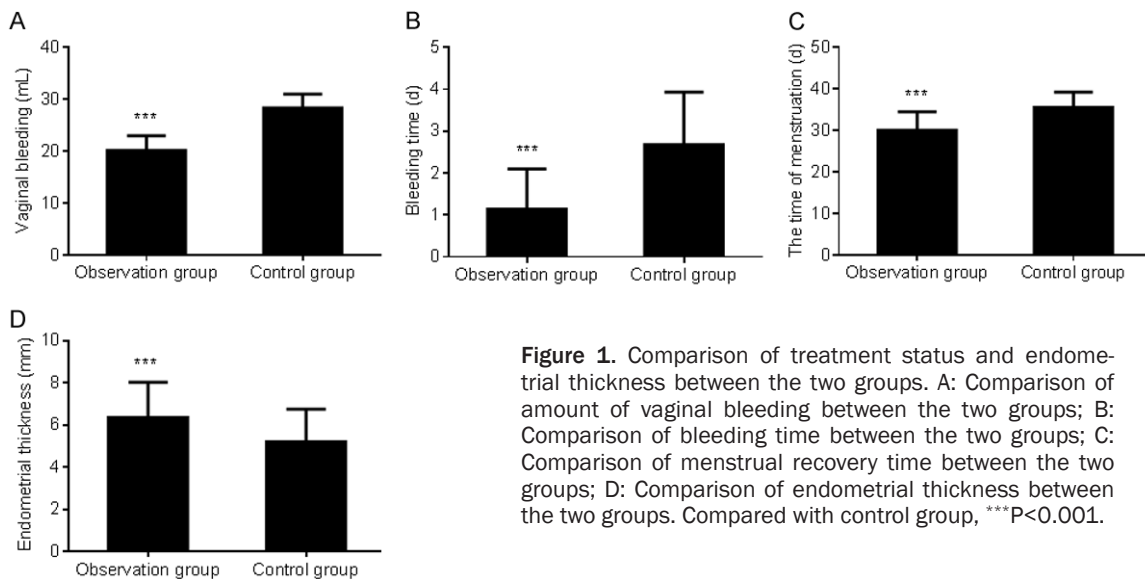


Figure 1. Comparison of treatment status and endometrial thickness between the two groups. A: Comparison of amount of vaginal bleeding between the two groups; B: Comparison of bleeding time between the two groups; C: Comparison of menstrual recovery time between the two groups; D: Comparison of endometrial thickness between the two groups. Compared with control group, ***P<0.001.

Table 3. Comparison of hemodynamic indexes between the two groups ($\bar{x} \pm s$)

Group	PI		RI		S/D	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group (n=44)	0.78±0.22	0.32±0.15***	2.86±1.04	1.28±0.75***	6.84±1.22	2.32±0.35***
Control group (n=42)	0.80±0.24	0.45±0.13***	2.91±1.17	1.67±0.62***	6.79±1.34	3.45±0.43***
t	0.403	4.286	0.210	2.622	0.181	13.394
P	0.688	0.000	0.834	0.010	0.857	0.000

Note: PI: pulsatility index; RI: resistance index; S/D: end arterial systolic/diastolic velocity ratio. Compared with the same group before treatment, ***P<0.001.

The observation group had significantly higher negative conversion time of HCG

The negative conversion rate of HCG in the observation group was higher than that in the control group at 1 and 2 weeks after treatment, with a significant difference (P<0.05). There was no significant difference in the negative conversion rate of HCG between the two groups at 3 weeks after treatment (P>0.05). See **Table 5**.

The observation group had significantly lower incidence of complications

The incidence of complications in the observation group was lower than that in the control group (P<0.05). See **Table 6**.

Discussion

There are many causes for missed abortions, and it is reported that 35.6% of missed abor-

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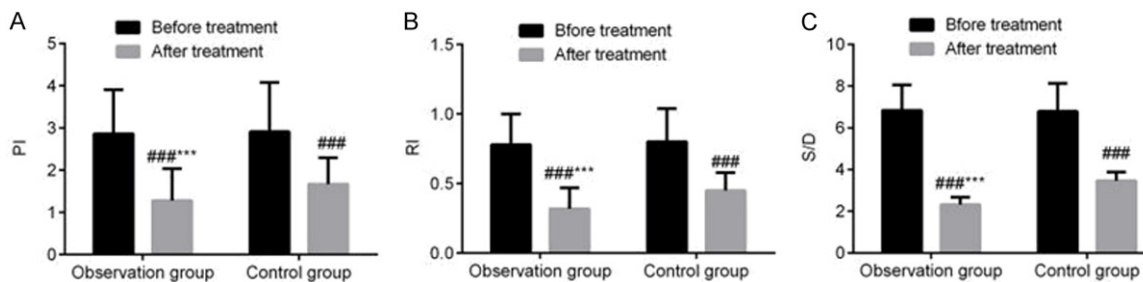


Figure 2. Comparison of hemodynamic indexes between the two groups. A: Comparison of PI between the two groups; B: Comparison of RI between the two groups; C: Comparison of S/D between the two groups. Compared with before treatment, $###P<0.001$; compared with control group, $*P<0.05$, $***P<0.001$. PI: pulsatility index; RI: resistance index; S/D: end arterial systolic/diastolic velocity ratio.

Table 4. Comparison of serum HIF-1 α and VEGF levels between the two groups ($\bar{x} \pm s$, ng/L)

Group	HIF-1 α		VEGF	
	Before treatment	After treatment	Before treatment	After treatment
Observation group (n=44)	312.53 \pm 90.80	109.95 \pm 23.69 $###$	36.69 \pm 3.71	29.92 \pm 2.18 $###$
Control group (n=42)	315.94 \pm 92.33	156.28 \pm 35.32 $###$	35.74 \pm 3.56	32.68 \pm 2.24 $###$
t	0.173	7.174	1.211	5.791
P	0.863	0.000	0.229	0.000

Note: HIF-1 α : hypoxia inducible factor 1 α ; VEGF: vascular endothelial growth factor. Compared with the same group before treatment, $###P<0.001$.

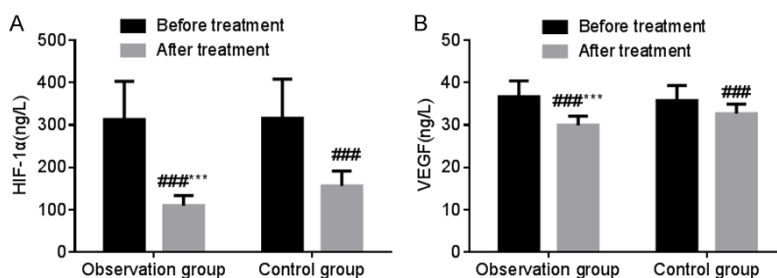


Figure 3. Comparison of serum HIF-1 α and VEGF levels between the two groups. A: Comparison of HIF-1 α levels between the two groups; B: Comparison of VEGF levels between the two groups. Compared with before treatment, $###P<0.001$; compared with control group, $***P<0.001$.

Table 5. Comparison of HCG negative conversion time between the two groups ($\bar{x} \pm s$)

Group	At 1 week	At 2 weeks	At 3 weeks
	after treatment	after treatment	after treatment
Observation group (n=44)	22 (50.00)	31 (70.45)	44 (100.00)
Control group (n=42)	11 (26.19)	18 (42.86)	40 (95.24)
χ^2	5.151	6.676	3.257
P	0.023	0.010	0.071

tions have unknown causes [11]. Among the unknown causes, it was found that abnormal uterine embryo circulation was an important cause of missed abortion, and the abnormal

expression of serum HIF-1 α and VEGF was closely related to missed abortion [12]. In recent years, with the increase of pollutants and the increase of elderly parturient, the incidence of missed abortion increases year by year. After the treatment of missed abortion, many complications such as intrauterine adhesions and cervical adhesions also appear. How to reduce these complications is still an urgent problem.

Mifepristone is a new synthetic anti progesterone. The mechanism of its treatment for missed abortion includes: affinity to progesterone receptors of the uterus, blocking the effect of progesterone, promoting decidual degeneration and necrosis; reducing the production of HCG, promoting corpus luteum dissolution, stimulating the increase of prostaglandin secretion, improving the sensitivity

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Table 6. Comparison of complications between the two groups [n (%)]

Group	Intrauterine adhesion	Hypomenorrhea	Abdominal pain	Total incidence rate
Observation group (n=44)	1 (2.27)	2 (4.55)	0 (0.00)	6.82
Control group (n=42)	7 (16.67)	8 (19.05)	5 (11.90)	47.62
χ^2				18.259
P				0.000

of uterine smooth muscle, softening the cervix; regulating the proportion of estradiol and progesterone, exciting the uterine muscle, promoting the contraction of the uterus, thus promoting the expulsion of embryos [13, 14]. Methyl carboprost suppository has the effect of exciting the uterine smooth muscle, thus promoting the rhythmic contraction of uterus, and accelerating the exfoliation and expulsion of embryo [15]. Transcutaneous electrical stimulation combined with mifepristone plus methyl carboprost suppository has the effect of synergistic enhancement, which can promote embryo expulsion and terminate pregnancy. Transcutaneous electrical stimulation is one of the modern physical therapies. It has many functions such as exciting muscles, promoting muscle contraction, analgesia, dilating blood vessels, exciting or inhibiting autonomic nerves, and is widely used in clinical practice [16]. The therapeutic effect of transcutaneous electrical stimulation is achieved by the “regulating Qi” and “treating spirit” functions of acupuncture points and the physiological effects such as the stimulation of nerve and muscle tissue by pulse electricity, the improvement of microcirculation, and the promotion of inflammatory substances absorption. The results of this study showed that the amount of vaginal bleeding, bleeding time, and menstrual recovery time in the observation group were less than those in the control group; after treatment, the endometrial thickness of the observation group was greater than that in the control group. This indicated that transcutaneous electrical stimulation combined with mifepristone plus methyl carboprost suppository can improve the curative effect, reduce vaginal bleeding and promote uterine recovery. The reason is probably that transcutaneous electrical stimulation combined with mifepristone plus methyl carboprost suppository can promote uterine contraction, reduce vaginal bleeding, improve local microcirculation of the uterus, promote menstrual onset and endometrial recovery [17].

A study has found that as the gestational weeks increase, uterine arterial blood flow also increases and the utero-gestational sac placental circulation continues to increase [18]. At the same time, relevant research has shown that the uterine hemodynamic indexes of the patients with missed abortion are different from those of the normal pregnant women, and the high resistance state of the uterine artery can increase the risk of abortion [19]. The results of this study showed that after treatment, PI, RI and S/D were decreased in the two groups, and PI, RI and S/D in the observation group were lower than those in the control group. This suggested that transcutaneous electrical stimulation combined with mifepristone plus methyl carboprost suppository can improve uterine artery blood flow and local hemodynamics, which was consistent with previous literature [20]. The reason is probably that after the embryo is delivered, the demand of uterine blood flow is reduced, so that PI, RI and S/D are reduced, and transcutaneous electrical stimulation is used to further improve the microcirculation of uterus, promote the recovery of uterus, so that PI, RI, S/D improvement is more clear.

HIF-1 α , a transcription factor, is readily degraded by the ubiquitin-proteasome pathway at normal oxygen concentrations; however, under the hypoxia environment, the stability and activity of HIF-1 α are enhanced, the survival time in cells is prolonged, and it can be transferred to the nucleus to combine with a coactivator, so that a series of reactions adapting to the hypoxia environment takes place in cells [21]. VEGF is a kind of mitogen that can participate in the new generation of blood vessels and promote angiogenesis [22]. Meanwhile, VEGF is also the target gene of HIF-1 α , which is regulated by HIF-1 α , hypoxia and ischemia, hormone fluctuation, hyperglycemia and other factors. In a hypoxic environment, serum VEGF expression is abnormally increased [23]. The mechanism of missed abortion caused by the decrease of serum HIF-

1α and VEGF may be that the transcriptional activator 2 negatively regulates the expression of HIF- 1α and decreases its expression, and the expression of VEGF is also decreased. Transcriptional activator 2 changes the oxygen deficient environment of the uterus and causes abortion by competing with HIF- 1α and binding its coactivator. Meanwhile, low expression of VEGF can lead to insufficient angiogenesis and increase the risk of abortion [24]. Relevant study has found that serum HIF- 1α and VEGF levels in patients with missed abortion are significantly lower than those in pregnant woman with live births and accidental pregnancy during the same period [25]. The results of this study showed that serum HIF- 1α and VEGF levels of the two groups were decreased after treatment, and the observation group was lower than that of the control group. It showed that transcutaneous electrical stimulation combined with mifepristone plus methyl carboprost suppository can reduce serum HIF- 1α and VEGF levels. The reason is probably that after treatment, the embryo is delivered, the hypoxia of the uterus is improved, and the HIF- 1α and VEGF levels are decreased. In addition, transcutaneous electrical stimulation therapy can improve the efficacy and further reduce the HIF- 1α and VEGF expression levels, which may also be an important mechanism for transcutaneous electrical stimulation combined with mifepristone plus methyl carboprost suppository to reduce vaginal bleeding and promote endometrial recovery in patients.

The results of this study showed that the negative conversion rate of HCG in the observation group at 1 and 2 weeks after treatment was higher than that in the control group, and the incidence of intrauterine adhesion, hypomenorrhea and abdominal pain in the observation group was lower than that in the control group, which was basically consistent with previous literature [26]. The results showed that transcutaneous electrical stimulation combined with mifepristone plus methyl carboprost suppository can promote the negative conversion of HCG and prevent complications. The reason is probably that transcutaneous electrical stimulation improves uterine microcirculation and promotes uterine recovery, thus increasing the negative conversion rate of HCG; at the same time, transcutaneous electrical stimulation promotes the flow of Qi and blood, unblocks the meridians, activates blood circulation and re-

moves blood stasis, promotes new blood generation, eliminates inflammation inside the uterus, and prevents complications such as adhesions and abdominal pain by reconciling Yin and Yang viscera. There are still some limitations in this study, such as small sample size and selection bias, which need to be further confirmed by enlarging the sample size and expanding the indications in the future.

In conclusion, transcutaneous electrical stimulation combined with mifepristone plus methyl carboprost suppository in the treatment of missed abortion can shorten the time of vaginal bleeding, reduce the amount of vaginal bleeding, and promote the increase of endometrial thickness. The mechanism may be related to the improvement of endometrial hemodynamic status and the down-regulation of serum HIF- 1α and VEGF expression levels.

Disclosure of conflict of interest

None.

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