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Clinical efficacy of levonorgestrel intrauterine system (Mirena) combined with hysteroscopy in the treatment of perimenopausal AUB patients

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Abstract: Perimenopausal abnormal uterine bleeding (AUB) is most common in ovulation dysfunction, which seriously compromises patients' health. This study aims to evaluate the efficacy of levonorgestrel intrauterine system (Mirena) plus hysteroscopy respectively in perimenopausal AUB. Sixty perimenopausal AUB patients treated with hysteroscopic electric resection in our hospital between January 2020 and December 2020 were enrolled and randomized to control group given dydrogesterone and study group treated with Mirena, with 30 cases in each group. The treatment efficacy, sex hormone level, hemoglobin (Hb) level, endometrial thickness and menstruation conditions were compared. The total efficacy was higher in the study group than that in the control group ($P<0.05$). The study group had lower follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E_2) levels and higher Hb levels compared with those of the control group (all $P<0.05$). Thinner endometrial thickness, lower pictorial blood loss assessment chart (PBAC) scores and shorter duration of menstruation were observed in the study group (all $P<0.05$). Both Mirena and dydrogesterone enhance the clinical efficacy of hysteroscopic treatment of perimenopausal AUB patients, with the advantages of Mirena being more promising.

Keywords: Perimenopausal abnormal uterine bleeding, hysteroscopy, dydrogesterone, levonorgestrel intrauterine system

INTRODUCTION

Abnormal uterine bleeding (AUB) is a common symptom of gynecology, which refers to abnormal bleeding from uterine cavity that is inconsistent with normal menstrual cycle frequency, regularity, length of menstrual period, and amount of menstrual bleeding (Benetti-Pinto *et al.*, 2017; Marnach and Laughlin-Tommaso, 2019). Perimenopause is a period in which ovarian function and estrogen level declines, leading to changes in biological, endocrine, and clinical symptoms (Delamater and Santoro, 2018). Abnormal uterine bleeding may occur at any age, with perimenopause being the most common period. Statistics have shown that AUB is one of the most frequent gynecological diseases in perimenopause, which accounts for 60-70% of all cases, with endometritis and endometrial hyperplasia as the major causes (Jewson *et al.*, 2020). The etiology of AUB in perimenopausal period is complicated (Sabbioni *et al.*, 2017; Chapagain and Dangal, 2020). Decreased hormone levels due to ovarian atrophy are the most common cause of ovulation abnormalities and endometrial lesions are also the main cause of perimenopausal AUB (Jetley *et al.*, 2013). Hysteroscopy reduces uterine bleeding by removing the entire endometrium and its superficial muscular layer with a high-frequency electric knife to cause scarring and fibrosis of the endometrium (Luterek *et al.*, 2014). Hysteroscopy, is gradually overtaking conventional ultrasound and diagnostic curettage as the current gold standard for clinical diagnosis of AUB with its merits of economy, safety and convenience. Dydrogesterone and levonorgestrel intrauterine system (Mirena) are the common drugs used in the treatment of AUB, while little has been reported about the use of both in hysteroscopic treatment (Wang *et al.*, 2020). The current research was designed to investigate the value of Mirena combined with hysteroscopy for clinical treatment of perimenopausal AUB.

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MATERIALS AND METHODS

General information

Sixty perimenopausal AUB patients treated with hysteroscopic electric resection in our hospital between January 2020 and December 2020 were enrolled and randomized to control group and study group, with 30 cases in each group. In the control group, patients were aged 45-59 years, with a mean of (53.09±4.24) years, the duration of bleeding was 2-8 months and endometrial thickness ranged from 10.5 to 16.8mm, with a mean of (13.84±2.27) mm. In the study group, patients were aged 46-57 years, with a mean of (52.87±4.30) years, the duration of bleeding was 2-10 months, and endometrial thickness ranged from 11 to 17.1mm, with a mean of (13.87±2.31) mm. The two groups presented no significant disparity in terms of general information ($P>0.05$). All patients voluntarily participated in the study and signed the informed consent form after being fully informed of the purpose and process of the study. This study was ethical approved by the Ethics Committee of

Yangzhou University (Approved No. of ethic committee: 2020-059-KY-331). The protocol in this study followed the World Medical Association Declaration of Helsinki (Ballantyne and Eriksson, 2019).

Inclusion and exclusion criteria

Inclusion criteria: 1) Patients who met the diagnostic criteria in the Expert Consensus on the Diagnosis and Treatment of Abnormal Perimenopausal Uterine Bleeding based on hysteroscopic findings (Singh *et al.*, 2013); 2) Patients with simple endometrial hyperplasia; 3) Patients in perimenopause; 4) Patients with no birth plan.

Exclusion criteria: 1) Patients with coagulation disorders; 2) Patients with severe genital disease, malignancy, or other organ dysfunction; 3) Patients with uterine bleeding caused by ectopic pregnancy or inflammatory reaction; 4) Patients who had been treated with hormonal drugs or other medications that may affect the study 14 days prior to enrollment; 5) Patients with cervical scarring and uterine hypertrophy.

Methods

All patients were treated with hysteroscopic electric resection. The surgery was performed within the second to fifth day after the menstrual period. After 8 hours of fasting and routine sterilization of the surgical site, epidural anesthesia was performed with the patients in a lithotomy position. 5% mannitol solution was used as the distending medium and the electrocautery perfusion rate was set to 300-450ml/min to maintain the dilation pressure around 100-150 mmHg and the power was set at 80 W. A cervical dilator was used to dilate the cervix, and a hysteroscope (Jiangsu Jiahua Electronic Equipment Co., Ltd., Model HJ-60) was placed to observe the uterine cavity. After identifying the lesion, loop electrosurgical excision procedure was performed on the endometrium and its associated myometrium using a 90° electric cutting loop, at the base of the uterine cavity to 5 mm above or below the cervical os and to a depth of 2-3 mm below the endometrium. In wake of the electric resection, Mirena (Bayer Healthcare Ltd. Guangzhou, China, NMPA Approval Number J20140088) was placed in the uterine cavity of patients in the study group, and the patients' conditions were closely monitored. The contraceptive system was removed immediately for patients with discomfort, and regular follow-up visits were conducted for patients without abnormalities, for whom Mirena was removed till the sex hormone levels have reached the corresponding level of the menopausal status. Patients in the control group were given oral administration of dydrogesterone (Abbott Biologicals B.V. NMPA Approval Number H20130110), 10mg/time, 2 times/d, for 7 consecutive days. The next course of treatment was started after the appearance of withdrawal bleeding and 3 consecutive courses of treatment were given.

Clinical efficacy

Three months after treatment, patients were reviewed to assess their treatment outcome. Efficacy criteria: In combination with the Expert Consensus on the Diagnosis and Treatment of Abnormal Perimenopausal Uterine Bleeding, patients were evaluated according to their clinical manifestations and laboratory test results. Markedly effective: If the uterine bleeding had ceased and the normal menstrual cycle was restored, as well as the normal volume and color of menstruation, the efficacy was considered markedly effective. If the uterine bleeding was reduced by ≥50%, a regular menstrual cycle was restored and the menstrual volume and color were largely normalized, the efficacy was considered effective. If no significant improvement in uterine bleeding, menstrual period, and menstrual volume were obtained, the efficacy was considered ineffective. Total efficacy = (number of cases with markedly effective + effective) / total number of cases *100%.

Laboratory index

Before and 3 months after treatment, 5ml of fasting venous blood was collected from patients and after routine treatment, the patients' hemoglobin (Hb) levels were determined by a Beckman Coulter IMMAGE 800 specific protein analyzer. In addition, 5ml of fasting venous blood was collected and centrifuged at 3000 r/min for 15 min, to determine the levels of serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E_2) using chemiluminescence immunoassay. The kits were manufactured by Wuhan Mind Bio-Technology Co., Ltd. and were operated in strict accordance with the kit instructions.

Endometrial thickness, PBAC and others

The endometrial thickness of the patients was measured before and after treatment using a color Doppler ultrasound diagnostic instrument (GE, model 730, USA). Referring to the relevant literature, the pictorial blood loss assessment chart (PBAC) (Hald and Lieng, 2014) score was used to assess patients' menstrual flow and to observe the degree of blood staining of sanitary napkins at the onset of menstruation, in which 1 point indicates that the blood-stained area was smalled than 1/3 of the sanitary napkin area, 5 points indicate that the blood-stained area was between 1/3 and 3/5 of the sanitary napkin area, and 20 points indicate that the blood-stained area basically covered the entire sanitary napkin. The duration of menstruation of the patients was also recorded. The patients were followed up for 3 months after treatment, and disease recurrence was counted in patients with effective and markedly effective efficacy.

STATISTICAL ANALYSIS

The data were analyzed using SPSS18.0 statistical software. The measurement data were expressed as mean ± standard deviation (±s), and t-test was used for

Table 1: Comparison of the efficacy of the two groups [n (%)]

Groups (n=30)	Markedly effective	Effective	Ineffective	Total effective rate
Study group	12(40.00)	16(53.33)	2(6.67)	28(93.33)
Control group	10(33.33)	12(40.00)	8(26.67)	22(73.33)
χ^2				4.320
P				0.038

Table 2: Comparison of sex hormone levels and Hb levels between the two groups (x ±s)

Groups (n=30)	FSH(mlU/ml)		LH(mlU/ml)		E_2(pmol/L)		Hb(g/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study group	38.26 ±7.81	12.50 ±4.06*	35.42 ±6.38	11.03 ±3.24*	385.64 ±29.37	212.45 ±20.84*	88.56 ±18.94	112.67 ±16.50*
Control group	36.89 ±7.65	15.81 ±4.17*	36.55 ±6.40	13.67 ±3.31*	386.17 ±28.21	235.67 ±22.06*	87.98 ±20.03	101.45 ±17.22*
t	0.627	2.843	0.625	2.849	0.065	3.821	0.105	2.352
P	0.472	0.006	0.473	0.006	0.875	0.002	0.812	0.009

Table 3: Comparison of endometrial thickness, menstrual volume and duration of menstruation between the two groups (x ±s)

Groups (n=30)	Endometrial thickness (mm)		PBAC score (point)		Duration of menstruation (d)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study group	11.05±2.12	4.35±1.60*	13.62±4.10	5.75±2.13*	9.50±1.52	5.51±1.25*
Control group	11.16±2.16	5.62±1.57*	13.55±4.14	8.50±2.25*	9.64±1.57	7.05±1.30*
t	0.182	2.833	0.060	4.293	0.320	4.269
P	0.801	0.005	0.877	0.001	0.651	0.001

Note: Compared with pre-treatment *P < 0.05.

comparison between two groups. The count data were expressed as [n(%)] and chi-square test was used for comparison between groups. The difference was considered statistically significant at P<0.05.

RESULTS

Therapeutic efficacy

Three months after treatment, the study group had 12 cases of markedly effective and 16 cases of effective, with a total efficacy of 93.33%. The control group had 10 cases of markedly effective and 12 cases of effective, with a total efficacy of 73.33%. The total efficacy was significantly higher in the study group compared with the control group (P<0.05), as shown in table 1.

Sex hormone levels and Hb levels

Before treatment, there was no significant disparity between the two groups in terms of FSH, LH, E2 levels, and Hb levels (P>0.05). After treatment, both groups had a decline in the sex hormone levels and an increase in the Hb levels, with lower sex hormone levels and higher Hb levels in the study group than the control group (P<0.05), as shown in table 2.

Endometrial thickness, menstrual volume and duration of menstruation

Before treatment, the two groups did not differ with regard to endometrial thickness, menstrual volume, PBAC score, and duration of menstruation (P>0.05). 3 months after treatment, the above indexes were improved remarkably (P<0.05). See table 3.

Short-term recurrence rate

After 3 months of follow-up, there was one case of recurrence among the patients with markedly effective and effective efficacy in the study group, with a recurrence rate of 3.57% (1/28) and one case of recurrence among the patients with markedly effective and effective efficacy in the control group, with a recurrence rate of 4.55% (1/22). The two groups showed no statistically significant difference in the short-term recurrence rate (χ2=0.030, P=0.861).

DISCUSSION

The progressive decline of ovarian function, metabolic imbalance and the massive secretion of sex hormones in perimenopausal women, coupled with the stimulation of

other external factors such as weather and emotions, can result in an imbalance in the regulation of the hypothalamic-pituitary-ovarian axis, thereby triggerring AUB (Talukdar and Mahela, 2016). The main manifestations of the disease include endometrial polyps, endometrial hyperplasia, and adenomyosis. A previous study found that in patients with AUB at different ages, the pathological manifestations vary to a certain extent, with cyclic endometrium being the most common manifestation at the age of 40-55 years, which is also known as perimenopause, followed by endometrial polyps and hyperplastic endometrial disorders (Nicula *et al.*, 2017). Therefore, an effective diagnosis for the treatment of perimenopausal AUB to clarify the pathological features is of great significance. In recent years, hysteroscopic technology is widely used in the diagnosis and treatment of AUB in light of its advantages of less trauma, better efficacy and faster postoperative recovery when compared with traditional surgical methods (Sinha *et al.*, 2018).

Hysteroscopic electric resection mainly involves the transcervical removal of the endometrium, to reduce the menstrual flow in perimenopausal AUB patients and avert long-term blood loss (Pandey *et al.*, 2017). However, the treatment outcome predisposes to be affected by the postoperative endometrium regeneration and intraoperative electrode destruction, which underlines the importance of progestin drugs as postoperative supplemental treatment in the hysteroscopic treatment of perimenopausal AUB patients. Currently, there are numerous studies related to dydrogesterone and Mirena in the treatment of AUB, in which many studies have concluded that Mirena outperforms other drugs in terms of clinical efficacy (Dhamangaonkar *et al.*, 2015). To further explore an optimal treatment regimen, the present study was conducted to compare the efficacy of dydrogesterone and Mirena in combination with hysteroscopy respectively in the treatment of perimenopausal AUB patients. Herein, patients treated with Mirena obtained a higher overall clinical efficacy when compared to those treated with dydrogesterone, which suggests that Mirena has a significant advantage in enhancing the efficacy of hysteroscopic treatment.

It has been reported that progestins are efficient in regulating intermenstrual bleeding or reducing heavy menstrual bleeding in women of childbearing age and perimenopausal women, with its efficiency in treating endometrial hyperplasia, especially in menopausal women (Schatz *et al.*, 2016). In the present study, both dydrogesterone and Mirena are progestins, of which dydrogesterone is an oral progestin with natural progesterone as the main component and its use in the treatment of perimenopausal AUB can induce the secretory phase and cyclic shedding of the endometrium, regulate the secretion of progesterone in the body, inhibit the endometrial hyperplasia or polyps triggered by long-term high estrogen stimulation and thus heal endometrial lesions (Cieraad *et al.*, 2006). Moreover, both regimens yielded desirable outcomes in the improvement of sex hormone levels, menstruation, and Hb levels, with better results observed in the groups given Mirena.

This is mainly due to the fact that Mirena, in contrast to the oral progestin, provides a higher local drug concentration in the endometrium than the blood circulation concentration by placing the progestin directly in the uterine cavity, allowing a full play of the drug effect, which subsequently induces endometrial glandular and interstitial metaplasia, which acts to inhibit endometrial proliferation and reduce endometrial thickness, thereb achieving a hemostatic effect. Besides, the levonorgestrel contained in Mirena, when placed in the uterine cavity, can be released in a sustained and slow manner, with a longer duration of action compared to dydrogesterone, allowing for better-targeted effects of the drug (Gemzell-Danielsson *et al.*, 2012). Mirena also directly regulates estrogen levels after placement, reduces estrogen stimulation of the endometrium, abates the sensitivity of the endometrium to E_2, lowers the menstrual volume, and shortens the duration of menstruation. Prior research has demonstrated that the levonorgestrel intrauterine system is the most cost-effective treatment regimen. The above results indicate a promising application value of Mirena in the treatment of AUB (Eralil, 2016). A previous study has compared dydrogesterone and Mirena in preventing the recurrence of endometrial polyps after hysteroscopy and found similar results between the two protocols (Zhao *et al.*, 2020). This study also compared the two drugs combined with hysteroscopy in the treatment of perimenopausal AUB and found that the short-term recurrence rate between the two groups was not significantly different and remained at a lower level, confirming that both dydrogesterone and Mirena have an excellent preventive effect on the recurrence of perimenopausal AUB after hysteroscopy.

CONCLUSION

The treatment efficacy of different drugs combined with hysteroscopy in the treatment of perimenopausal AUB patients varies to a certain extent, and Mirena yields superior efficacy in the hysteroscopic treatment of perimenopausal AUB patients to dydrogesterone.

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