Research Paper

# Clinical Efficacy of Medroxyprogesterone Combined with Different Antibiotics in the Treatment of Chronic Endometritis

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**The objective of this study was to determine the clinical value of medroxyprogesterone combined with different antibiotics in the treatment of chronic endometritis. A total of 320 subjects were selected and divided into study group and control group according to odd and even numbers, with 160 subjects in each group. The control group was treated with combination of antibiotics and the research group was given medroxyprogesterone on the basis of the control group. The medication cycle is 5 d. A comparative study was carried out on the effects of medication between the two groups. After medication, the total effective rate of patients in the study group was 94.37 %, significantly higher than 75.63 % in the control group ($p<0.05$). The levels of inflammation in both groups were reduced, but the research group was significantly better than the control group ($p<0.05$). The endometrial thickness and uterine recovery time in the study group were significantly better than those in the control group ($p<0.05$), while the sex hormone levels and irregular vaginal bleeding rate in the study group were significantly lower than those in the control group ($p<0.05$). The normal rate of menstruation and quality of life scores in the study group were significantly higher than those in the control group ($p<0.05$), and there was no significant difference in adverse drug reactions between the two groups ($p>0.05$). Progesterone combined with different antibiotics has a significant effect on chronic endometritis, which can reduce the level of inflammation, increase the thickness of endometrium, improve the level of uterine status and normal menstruation rate, reduce the level of sex hormones and the rate of irregular vaginal bleeding, etc. It has a good effect, high drug safety, helps to improve the quality of life and is worthy of popularization.**

**Key words: Medroxyprogesterone, metronidazole, cefmetazole sodium, chronic endometritis, drug efficacy**

Chronic Endometritis (CE) is an inflammatory condition that occurs in the lining of the uterus. The clinical manifestations of CE are abnormal uterine bleeding, lumbar soreness, pelvic pain and increased leucorrhea. The pathogenesis of CE is mainly related to the infection with pathogenic bacteria. Some studies have found that the microorganisms detected in the endometrium of CE patients mainly include *Streptococcus*, *Escherichia coli*, *Chlamydia*, *Mycoplasma*, anaerobic bacteria, *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Gardnerella vaginalis*, *Neisseria gonorrhoeae*, *Bacillus vaginalis*, etc. If CE is not treated in time, it will affect the health of women[1]. At present, the medications for CE mainly include hormonal drugs such as dydrogesterone and medroxyprogesterone, antibiotic drugs such as levofloxacin, cephalosporin, ornidazole, metronidazole, penyanjing, etc. Dydrogesterone is a reverse progesterone derivative derived from natural progesterone without the effects of estrogens, androgens and adrenocorticoids. Dydrogesterone can make the endometrium reach a complete secretory phase, repair the endometrium and reduce the risk of inflammatory cell infiltration[2]. At present, Chinese researchers have little research on the treatment of CE with dydrogesterone. Progesterone has been used clinically for decades. It is classified as a progesterone-like derivative of 17-alpha (α)-hydroxyprogesterone, which is a synthetic luteal progestogen and is mainly used to treat gynecological diseases. Progesterone has a very good effect on CE. According to the research, progesterone can directly act on the endometrium and

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combine with progesterone receptors, leading to the gradual reduction of the uterus in the proliferative period and the shedding of the endometrium[3]. The *in vitro* antibacterial activity of levofloxacin is twice that of ofloxacin for the treatment of CE. Its mechanism of action is to prevent the synthesis and replication of bacterial Deoxyribonucleic Acid (DNA) by inhibiting the activity of DNA gyrase in bacteria[4].

Levofloxacin shows antibacterial effect on most Gram-positive and Gram-negative bacteria and it can also show antibacterial effect on various types of *Chlamydia* and *Mycoplasma*, but its effect on anaerobic bacteria and enterococci is poor. Antibiotic ornidazole belongs to the third generation of nitroimidazole derivatives, which mainly acts on infections caused by sensitive protozoa and anaerobic bacteria. Cephalosporins have broad-spectrum characteristics in the process of bacterial inhibition and their basic pharmacology is that they can have strong inhibitory effect on bacterial beta (β)-lactamases. Metronidazole is a nitroazole derivative, which can block the synthesis of bacterial nucleic acid in the body and can effectively inhibit the growth and reproduction of bacteria, reduce the number of bacteria and can remove vaginal bacteria by showing a strong antibacterial and anti-inflammatory effect by enhance the secretion of anti-inflammatory factors like Interleukin-2 (IL-2). Cefmetazole sodium is a second-generation cephalosporin broad-spectrum antibacterial drug, which can show a good antibacterial effect on a variety of Gram-positive, Gram-negative bacteria and anaerobic bacteria. In this study, the use of progesterone combined with metronidazole, cefmetazole sodium and other antibiotics to treat CE was compared with only metronidazole and cefmetazole sodium antibiotics.

## MATERIALS AND METHODS

### General information:

The research data obtained from 320 CE patients who were treated in our hospital from January 2020 to June 2022 were divided into study group and control group by using odd and even visit numbers, with 160 patients in each group. The average age of the study group was (38.26±3.42) y and the average disease duration was (4.72±1.24) mo. The mean age of the control group was (38.53±3.45) y and the mean disease duration was (4.71±1.23) mo. The clinical manifestations of all patients were increased leucorrhea (watery, dark or bloody) accompanied by severe lower abdominal pain and some patients had symptoms such as fever and enlarged uterus. There was no significant difference in the general information of the two groups of patients ($p>0.05$) and a comparative study after treatment can be carried out.

**Inclusion criteria:** Combined with clinical manifestations, hysteroscopy, routine blood examination of inflammatory response indicators, etc. were also diagnosed as CE by our hospital. Patients agreed to the purpose of this study and signed an informed consent and did not receive other drug treatment within 30 d.

**Exclusion criteria:** Patients with mental illness, diabetes, heart disease or other serious liver and kidney diseases are excluded. Patients with malignant tumors, immune system diseases and patients during breastfeeding and pregnancy are also excluded to participate in the study.

### Research methods:

The control group was given metronidazole injection (Manufacturer: Changchun Dazheng Pharmaceutical Co., Ltd., approval number: H22022423) intravenously. The standard injection volume for the first time was 15 mg/kg and the maintenance dose was 7.5 mg/kg, 3 times a day. In addition, intravenous drip was given by dissolving 1-2 g of cefmetazole sodium injection (Manufacturer: Hainan Tianhuang Pharmaceutical Co., Ltd., approval number: H20103098, specification: 0.5 g×480 tubes/piece) in 250 ml of sodium chloride solution, 3 times a day and continuously for 5 d.

On the basis of the control group, the research group was injected with medroxyprogesterone intravenously. Progesterone is produced by Zhejiang Xianju Pharmaceutical Co., Ltd., with approval number H33020823, and its specification is 1 ml:10 mg×10 sticks. Each injection is 10 mg, once a day, continuously for 5 d.

### Research indicators and evaluation criteria:

The research indicators mainly include the clinical effect after medication, inflammation level before and after medication, endometrial thickness, uterine recovery time, sex hormone level, normal menstruation rate, irregular vaginal bleeding rate and quality of life score, etc.

The clinical effects of medication are divided into three categories-markedly effective, improved and ineffective. Markedly effective category showed significant symptoms which include increased leucorrhea, abnormal color, lower abdominal pain and other symptoms completely disappeared, menstruation returned to normal and blood routine returned to normal. Improved category showed symptoms such as increased leucorrhea, abnormal color, lower abdominal pain and other symptoms have been improved to a certain extent, menstruation is basically normal and blood routine is basically normal. Ineffective category showed symptoms with little to no change compared with before the medication.

Total effective rate=marked rate+improvement rate

Fasting venous blood was drawn from the two groups of patients before and after medication and the level of Tumor Necrosis Factor-α (TNF-α), Interleukin-1 (IL-1) and IL-2 was detected by the laboratory. The high value indicates that the effect of medication is better.

The endometrial thickness was detected by Bright scan ultrasound (B-ultrasound) before and after treatment. Because the thickness of the endometrium is affected by multiple factors such as ovulation period and menstruation, in order to ensure the reliability of the research, the endometrial thickness was examined 5 d after menstruation. In this study, a higher value of endometrial thickness was regarded as a better drug effect.

The recovery time of the uterine includes the time of pelvic pain, time of leucorrhea increase and disappearance and the time of body temperature returning to normal, etc. In this study, the lower the value of these three indicators is regarded as the better curative effect.

Sex hormone levels are determined before and after medication. Fasting venous blood was collected and the laboratory department of the hospital used chemiluminescence immunoassay to measure the levels of Luteinizing Hormone (LH), Follicle-Stimulating Hormone (FSH) and Estradiol (E2) in the patient's body. In this study, the lower the values of these three indicators are regarded as the better the drug effect.

Menstrual conditions include the rate of normal menstruation and irregular vaginal bleeding. In this study, the higher the rate of normal menstruation and the lower the rate of irregular vaginal bleeding indicates, the better the drug effect.

In this study, the health status questionnaire 36-item Short Form (SF-36) survey was used to judge the quality of life of both the groups of patients before medication and 3 mo after the end of medication. The questionnaire included Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH) status, Vitality (VT), Social Functioning (SF) status, Role Emotional (RE) and Mental Health (MH). In this study, the higher the score of each index, the better the drug effect.

**Statistical analysis:**

All the data collected in this study were uniformly processed using Statistical Package for Social Sciences (SPSS) 20.0 software and the t test was used for comparison between the two groups and the difference $p<0.05$ was regarded as statistically significant.

## RESULTS AND DISCUSSION

Potential drug targets of puerarin were shown in Table 1. After medication, drug efficacy was compared between the two groups. 99 patients in the study group showed marked effective improvement, 52 patients showed improvement and the total effective rate was 94.37 %, which was significantly higher than that of the control group (75.63 %) ($p<0.05$) (Table 1).

Before the treatment, there was no significant difference in the indexes of inflammatory factors between the two groups ($p>0.05$). After the treatment, the values of IL-1 and TNF-α in the study group were lower and the values of IL-2 were higher and there was a significant difference between the two groups ($p<0.05$) (Table 2).

There was no significant difference in endometrial thickness between the two groups before treatment ($p>0.05$). After treatment, the endometrial thickness value of the study group was lower ($p<0.05$) (Table 3).

After medication, the duration of pelvic pain, leucorrhea increase and disappearance time, and uterine recovery time in the study group were significantly shorter than those in the control group ($p<0.05$) (Table 4).

Before medication, there was no significant difference

in the indicators of sex hormones between the two groups (p>0.05). After medication, the values of indicators of sex hormones in the study group were significantly lower than those in the control group (p<0.05) (Table 5).

After medication, the normal menstrual recovery rate of the study group was significantly higher than that of the control group, and the irregular vaginal bleeding rate was significantly lower than that of the control group (p<0.05) (Table 6).

Before medication, there was no significant difference in the scores of the quality of life indicators between the two groups (p>0.05). After medication, the scores of the quality of life indicators in the study group were significantly higher than those in the control group (p<0.05). This shows that the study group was superior to the control group in terms of improving the quality of life of patients (Table 7).

The adverse reaction rates of patients in the study group and the control group were 3.75 % and 3.125 %, respectively and there was no significant differences between the two groups (Table 8).

**TABLE 1: COMPARISON OF DRUG EFFECTS BETWEEN THE TWO GROUPS OF PATIENTS (x̄±s)**

| Group | n | Markedly effective | Improved | Ineffective | Total effective rate |
|---|---|---|---|---|---|
| Research | 160 | 99 (61.88 %) | 52 (32.5 %) | 9 (5.63 %) | 94.37 % |
| Control | 160 | 70 (43.75 %) | 51 (31.86 %) | 39 (24.36 %) | 75.63 % |
| $\chi^2$ | | | | | 5.92 |
| p | | | | | <0.05 |

**TABLE 2: COMPARISON OF INFLAMMATORY FACTORS IN THE TWO GROUPS OF PATIENTS BEFORE AND AFTER TREATMENT (x̄±s)**

| Group | n | IL-1 (pg/ml) | | IL-2 (pg/ml) | | TNF-α (pg/ml) | |
|---|---|---|---|---|---|---|---|
| | | Before medication | After medication | Before medication | After medication | Before medication | After medication |
| Research | 160 | 379.45±36.32 | 234.46±22.82 | 478.36±42.51 | 626.94±51.17 | 82.52±6.86 | 41.38±4.12 |
| Control | 160 | 378.64±36.44 | 278.53±24.84 | 477.28±42.71 | 562.36±45.56 | 82.46±6.72 | 61.24±5.36 |
| t | | 0.238 | 2.216 | 0.211 | 2.092 | 0.192 | 4.684 |
| p | | >0.05 | <0.05 | >0.05 | <0.05 | >0.05 | <0.05 |

**TABLE 3: COMPARISON OF EFFECT OF DRUGS ON ENDOMETRIAL THICKNESS IN TWO GROUPS (x̄±s)**

| Group | n | Endometrial thickness (cm) | |
|---|---|---|---|
| | | Before medication | After medication |
| Research | 160 | 0.51±0.11 | 0.3±0.07 |
| Control | 160 | 0.51±0.1 | 0.26±0.06 |
| t | | 0.094 | 6.285 |
| p | | >0.05 | <0.05 |

**TABLE 4: COMPARISON OF UTERINE RECOVERY TIME BETWEEN THE TWO GROUPS OF PATIENTS AFTER TREATMENT (x̄±s)**

| Group | n | Pelvic pain time (d) | Increased leucorrhea and disappearance time (d) | Body temperature back to normal time (d) |
|---|---|---|---|---|
| Research | 160 | 5.36±1.35 | 7.86±1.38 | 4.62±1.15 |
| Control | 160 | 8.29±1.76 | 10.26±2.13 | 5.82±1.35 |
| t | | 6.272 | 4.185 | 1.292 |
| p | | <0.05 | <0.05 | <0.05 |

**TABLE 5: COMPARISON OF SEX HORMONE LEVELS IN THE TWO GROUPS BEFORE AND AFTER TREATMENT (x̄±s)**

| Group | n | LH (U/l) | | FSH (U/l) | | E2 (pmol/l) | |
|---|---|---|---|---|---|---|---|
| | | Before medication | After medication | Before medication | After medication | Before medication | After medication |
| Research | 160 | 6.41±0.72 | 5.86±0.52 | 4.31±0.47 | 3.19±0.36 | 221.85±17.52 | 136.54±12.95 |
| Control | 160 | 6.42±0.72 | 6.12±0.61 | 4.31±0.46 | 3.84±0.41 | 220.62±17.43 | 186.66±14.28 |
| t | | 0.125 | 1.254 | 0.092 | 1.886 | 0.162 | 3.254 |
| p | | >0.05 | <0.05 | >0.05 | <0.05 | >0.05 | <0.05 |

**TABLE 6: COMPARISON OF THE MENSTRUAL STATUS OF THE TWO GROUPS OF PATIENTS AFTER MEDICATION (CASES, %)**

| Group | n | Menstruation returns to normal | Irregular vaginal bleeding |
|---|---|---|---|
| Research | 160 | 109 (68.13) | 8 (5) |
| Control | 160 | 42 (26.25) | 17 (10.63) |
| t | | 19.285 | 16.176 |
| p | | <0.05 | <0.05 |

**TABLE 7: COMPARISON OF QUALITY OF LIFE SCORES BETWEEN THE TWO GROUPS BEFORE AND AFTER TREATMENT (x̄±s)**

| Project | Time | Research group (n=160) | Control group (n=160) | t | p |
|---|---|---|---|---|---|
| PF | Before medication | 50.27±2.86 | 50.41±2.61 | 0.183 | >0.05 |
| | After medication | 89.32±4.21 | 72.14±3.91 | 2.682 | <0.05 |
| RP | Before medication | 51.14±3.06 | 51.21±3.07 | 0.182 | >0.05 |
| | After medication | 88.62±4.28 | 73.28±4.17 | 2.129 | <0.05 |
| BP | Before medication | 51.25±2.91 | 51.28±2.89 | 0.181 | >0.05 |
| | After medication | 90.04±2053 | 78.35±3.34 | 1.858 | <0.05 |
| GH | Before medication | 49.78±2.85 | 49.52±2.81 | 0.183 | >0.05 |
| | After medication | 90.12±3.31 | 79.78±3.36 | 1.788 | <0.05 |
| VT | Before medication | 51.09±3.25 | 51.11±3.31 | 0.182 | >0.05 |
| | After medication | 89.82±2.18 | 81.02±2.26 | 1.586 | <0.05 |
| SF | Before medication | 50.08±1.98 | 50.11±2.01 | 0.182 | >0.05 |
| | After medication | 88.63±2.43 | 76.51±3.08 | 1.924 | <0.05 |
| RE | Before medication | 52.28±2.37 | 52.31±2.36 | 0.181 | >0.05 |
| | After medication | 87.85±2.92 | 78.83±3.16 | 1.392 | <0.05 |
| MH | Before medication | 51.38±2.52 | 51.61±2.51 | 0.183 | >0.05 |
| | After medication | 90.18±2.42 | 80.15±2.18 | 1.724 | <0.05 |

**TABLE 8: COMPARISON OF ADVERSE DRUG REACTIONS BETWEEN THE TWO GROUPS OF PATIENTS (n, x̄±s)**

| Group | n | Increased fatigue | Drowsiness | Dizziness nausea | Intestinal discomfort | Total incidence |
|---|---|---|---|---|---|---|
| Research | 160 | 2 (1.25) | 2 (1.25) | 1 (0.625) | 1 (0.625) | 6 (3.75) |
| Control | 160 | 2 (1.25) | 1 (0.625) | 1 (0.625) | 1 (0.625) | 5 (3.125) |
| $\chi^2$ | | | | | | 0.723 |
| p | | | | | | >0.05 |

CE will not only affect the quality of oocytes and embryos, but also cause endometrial abnormalities which will reduce the effect of embryo implantation. CE induces the abnormal expression of immune cells and immune factors due to the infection or imbalance of microorganisms in the endometrial cavity, resulting in abnormal immune responses of the endometrium. These factors may cause repeated implantation failures and recurrent miscarriages[5]. At present, there are many treatment methods for CE, mainly including antibiotic drug treatment, endometrial stimulation therapy, intrauterine perfusion, stem cell and immunotherapy, etc. Although antibiotics are currently the most widely used method for the treatment of CE, there is no universally accepted protocol for antibiotic selection, dosage and duration of medication. The endometrium of CE patients is rich in variety of microorganisms and the composition of the pathogenic microorganisms is still unclear. In addition, antibiotics are generally only effective against certain types or type of bacteria and there are always doubts about the prognosis of CE. Therefore, in the actual course of medication, combination of multiple antibiotics is often used such as cephalosporin combined with metronidazole and so on. Taking this study as an example, metronidazole combined with cefmetazole sodium was used to treat CE. Metronidazole is currently accepted for the treatment of anaerobic infections, which is a broad-spectrum anti-anaerobic drug. It can resist anaerobic bacteria and can also inhibit the synthesis of bacterial DNA, hinder the growth and reproduction of bacteria and achieve the purpose of killing bacteria. The nitro group present in metronidazole can be reduced to an amino group in an oxygen-free environment, thereby achieving the effect of anti-anaerobic bacteria[6]. As mentioned above, there are multiple microorganisms in the endometrium of CE patients and the main drug effect of metronidazole can only kill anaerobic bacteria, which are only a small part of the microorganisms in the endometrium of CE patients. Therefore, from this perspective, the effect of metronidazole on CE patients is extremely limited. Cefmetazole sodium, as a second-generation cephamycin drug, has a certain curative effect on various anaerobic bacteria and Gram-negative bacteria and has a high sensitivity effect on Extended-Spectrum Beta-Lactamases (ESBLs)-producing *Escherichia coli* and *Klebsiella pneumoniae*. Studies have found that many physicians regard cefmetazole sodium as a perioperative antibiotic prophylaxis, resulting in unreasonable applicability of the drug[7]. Theoretically speaking, cefmetazole sodium targets more types of bacteria and its effect on CE will be better. In one study, 17.6 % of CE patients had plasma cell infiltration in the endometrial stroma after administration of antibiotics[8]. This study suggests that antibiotics are not effective in treating all CE patients and other mechanisms may be involved in the endometrial plasma cell infiltration in those patients. Some scholars have pointed out that the combined abuse of different antibiotics may lead to disorder of the immune system[9].

Progesterone, as a kind of progestogen drug, is convenient to take. After oral administration, it can regulate the level of progesterone in the patient's body, thereby resisting the long-term action of estrogen on the endometrium and regulating uterine function. As a progestogen drug, medroxyprogesterone is often used in dysfunctional uterine bleeding, CE, endometriosis, endometrial cancer and other conditions such as shedding, proliferation and menstrual repair[10]. The mechanism of medroxyprogesterone in treating abnormal uterine bleeding is that a large amount of high-efficiency progesterone causes endometrial atrophy and prevents the function of local blood vessels in the endometrium and thereby the microenvironment of the uterus is improved by promoting blood coagulation. Studies have shown that medroxyprogesterone can change the internal microenvironment of the uterus in patients with abnormal uterine bleeding and the growth factors in the uterine microenvironment are closely related to the levels of receptors and vasoactive substances in it[11]. Therefore, some scholars deduce from this that medroxyprogesterone achieves the purpose of hemostasis by affecting the microenvironment of the endometrium[12]. Studies have shown that medroxyprogesterone can directly antagonize the hyperplasia of ectopic endometrial tissue, change the expression of endocrine in the body and inhibit the activation of lymphocytes, thereby reducing the expression level of cytokines in the endometrium[13].

In this study, the efficacy of medication in the study group was better than that in the control group, which might be due to the drug effect of medroxyprogesterone. The level of inflammatory factors in the study group was better than that in the control group, which may be due to the progesterone antagonizing the hyperplasia of endometrium in ectopic growth and reducing the expression level of

cytokines in the endometrium. The improvement in endometrial thickness, uterine recovery time and sex hormone levels in the study group was better than that in the control group, which may be because medroxyprogesterone changed the progesterone level in the patient's body and promoted changes in uterine function. Antibiotics do not essentially change the progesterone levels in the patient's body. The quality of life score of patients in the research group is better than that of the control group. The research group is better than the control group in many previous indicators, and these indicators themselves act on the indicators of the quality of life score. In this study, the medication of the study group did not improve the menstrual status of the patients ideally and the menstrual recovery rate was 68.13 %. It may be related to the short duration of medication and future studies may consider extending the medication cycle, etc.

In this study, medroxyprogesterone combined with different antibiotics has a good effect on the treatment of CE and can improve the quality of life of patients, which is worthy of promotion.

**Conflict of interests:**

The authors declared no conflict of interest.

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