Clinical comparison of mifepristone and gestrinone for laparoscopic endometriosis

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Abstract: Endometriosis is a common disease among women of childbearing age, and it is the main cause of dysmenorrhea and infertility. This article analyzes the efficacy of mifepristone and gestrinone in the treatment of endometriosis. The results showed that the recurrence rate of mifepristone group and gestrinone group were 8.33% and 5%, respectively, which was significantly lower than 23.33% of the control group. Before and after treatment, LH, endocrine test results FSH, PRL had no obvious change in mifepristone group and gestrinone group, while E2 decreased, as mifepristone group (141.7±31.2) pmol/L, gestrinone group (64.2±11.7) pmol/L. The incidence of adverse reactions and liver dysfunction in the mifepristone group were significantly lower than those the gestrinone group (P<0.05). Mifepristone and gestrinone can be used for endometriosis postoperative adjuvant treatment, is safe and effective, but using mifepristone has the lower rate of adverse reaction. In conclusion, mifepristone is a current research focus, its mechanism of action in the process of exploration, has broad prospects in the treatment of endometriosis, its long-term application security is paid more and more attention.

Keywords: Mifepristone, endometriosis, clinical efficacy, hormone level, gestrinone.

INTRODUCTION

In recent years, its incidence increased year by year (Rafique et al., 2017). The disease is a benign lesion with metastasis and implantation characteristics, treatment more difficult (Yu et al., 2016). In the past, surgery was the main treatment. But the disease is easy to relapse after surgery. The application of adjuvant therapy may help stabilize postoperative efficacy, improve the prognosis (Rivosecchi et al., 2014). At present, the treatment of endometriosis with infertility is mainly treated with two kinds of medical treatment and surgical treatment, of which surgical treatment can relieve the pain of the patients, but the surgical trauma is larger and the postoperative recurrence is easy (Taylor et al., 2017). Traditional drug therapy can relieve the symptoms of endometriosis and improve the outcome of pregnancy. Mifepristone and gestrinone are the main drugs for the treatment of endometriosis (Salengros et al., 2010).

At present, gestrinone and mifepristone are the most frequently used drugs. Mifepristone is a synthetic 19- to methyl testosterone derivatives, mainly through the estrogen receptor and progesterone receptor down-regulation in ectopic endometrium, the ectopic endometrial degradation to achieve the treatment of endometriosis objective (Tosti et al., 2017). Mifepristone inhibits ovulation, induces corpus luteum dissolution and interferes with endometrial integrity. It is a progesterone antagonist, which can directly act on ectopic endometrium, inhibit its proliferation and differentiation, promote apoptosis, reduce its growth potential, effectively control endometriosis and reduce its recurrence (Vercellini et al., 2014). Adhesion of endometriosis is common in laparoscopy and it is difficult to remove thoroughly during ectopic cyst separation because of its easy separation (Yu et al., 2016). Surgical treatment can only remove the endometriosis, which can be identified by the naked eye. For the microscopic lesions, atypical lesions that can not be completely removed, the recurrence of the lesion can not be cleared after the operation (Taylor et al., 2017). After the operation, 3~6 months of medication can be given to the atrophy of the unresectable or deep unresectable lesions (Salengros et al., 2010). Therefore, it can prevent or delay the recurrence of the disease. Gestrinone main effect on endometrium and ectopic endometrium may play anti estrogen receptor and progesterone resistance strong, thus reducing the level of estrogen, but also with androgenic activity, can inhibit gonadotropin release, secretion of ovarian suppression, the ectopic endometrial atrophy (Goldstone et al., 2017).

To further explore the effective method for the treatment of severe endometriosis, at the same time in our hospital laparoscopic surgery for severe endometriosis patients, we analyzed treatment effect after surgery using mifepristone or gestrinone.

MATERIALS AND METHODS

Research object
180 patients with endometriosis from January 2016 to December 2017 in our hospital were randomly divided

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The patients in the control group did not give any drugs; the mifepristone group was treated with laparoscopic surgery as compared with the control group. Mifepristone group was given mifepristone for one week after operation, and 1 times/day, 10mg each time, oral administration for 6 months. Patients in group gestrinone were treated with laparoscopy and control group. In gestrinone group, gestrinone was given a week after operation, orally, two times a week, once 2.5mg, for 6 months. Three groups of patients were reexamined after laparoscopic surgery, and every three months. The review is to understand the patient's symptoms, signs, results of B-ultrasound etc. In mifepristone group and gestrinone group of patients during the treatment, is required for a visit every month, the main purpose of the visit is to understand the adverse drug reactions and follow-up in patients with liver function.

Observation index
The criteria of efficacy: (1) Relief: no symptoms, no signs, and found no pelvic masses; (2) improvement: Although there are primary symptoms, but the degree of symptoms was reduced, compared with before treatment reduced or no positive signs, and found no pelvic masses; (3) recurrence: Ultrasonography again found pelvic endometriosis cysts, or recurrence of symptoms and signs before treatment. And the incidence of liver function damage records of mifepristone group and gestrinone group of adverse drug reactions.

Adverse reaction
(1) Androgen like effects: Weight gain, hairy, voice changes, acne, seborrhoeic dermatitis, etc. (2) Low estrogen: bleeding, hot flashes, sweating, irritability, etc. (3) Liver dysfunction: elevated transaminase. (4) Gastrointestinal reaction: Upper abdominal discomfort, nausea and vomiting, fatigue and so on.

STATISTICAL ANALYSIS
Statistical analysis was carried out using SPSS14.0 software, the measurement data using mean and standard deviation (x±s), compared with two groups of data of mean t test, count data using χ2 test, P<0.05, the difference was statistically significant.

RESULTS
Comparison of the clinical efficacy of three groups of patients after treatment
The recurrence rates of mifepristone group and gestrinone group were 8.33% and 5% respectively, which were significantly lower than the control group 23.33%, the difference was statistically significant (P<0.05); The total effective rate in mifepristone group and gestrinone group was significantly higher than that in the control group (P<0.05). The total effective rate in mifepristone group was 91.66%, and the recurrence rate was 8.33%; while the total effective rate in gestrinone group as 95% and recurrence rate was 5%. The difference was not statistically significant (P>0.05), as shown in table 1.

Hormone level comparison
The two groups before and after treatment, LH, endocrine test results FSH PRL had no obvious change; E2 decreased as the mifepristone group (141.7±31.2) pmol/L, gestrinone group (64.2±11.7) pmol/L, but were in the early levels of follicles, no significant differences between the two groups. The endocrine results of mifepristone group and gestrinone group before and after treatment were shown in table 2.

Serum ovarian cancer associated antigen
Serum levels of ovarian cancer associated antigen (CA125) and liver function were measured. After three groups of treatment, CA125 was lower than before treatment. Compared with the laparoscope group, the difference between mifepristone and Gestrinone group decreased significantly (P<0.05), but there was no statistical difference between group Gestrinone and mifepristone group (P>0.05). The data is shown in table 3.

Adverse reaction
In the mifepristone group, there were 5 patients with...
abnormal liver function and the liver enzymes were slightly increased. The liver function recovered to normal after the treatment of unstopped medicine and with the treatment of liver protection. In group gestrinone, 17 cases were damaged, and most of the liver enzymes were significantly increased. The liver function recovered to normal after stopping and combining with the treatment of liver protection. The incidence of adverse reactions and liver function damage in mifepristone group were significantly lower than those in group gestrinone (P<0.05). The adverse reactions after medication were compared as shown in Table 5.

**DISCUSSION**

There are many treatments for endometriosis (EM), including drug therapy, surgery or surgery combined with drug therapy (Bhatt et al., 2015). In recent years, with the new understanding and deepening of the pathogenesis of EM, there have been many new developments in the adjuvant regimens before and after operation. Traditional drugs including "tatazol, Gn RH-a" and so on have been severely restricted due to severe side effects and expensive prices (Bergström et al., 1967; Carbonell et al., 2012). In recent years, the application of gestrinone in the

**Table 1**: Comparison of the clinical efficacy of three groups of patients after treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>Relieve</th>
<th>Improve</th>
<th>Recrudescence</th>
<th>Total effective rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mifepristone group</td>
<td>60</td>
<td>35(58.33)</td>
<td>20(33.33)</td>
<td>5(8.33)</td>
<td>91.66%</td>
</tr>
<tr>
<td>Gestrinone group</td>
<td>60</td>
<td>34(56.66)</td>
<td>23(38.33)</td>
<td>3(5.0)</td>
<td>95.0%</td>
</tr>
<tr>
<td>Control group</td>
<td>60</td>
<td>18(30.0)</td>
<td>28(46.66)</td>
<td>14(23.33)</td>
<td>76.66%</td>
</tr>
</tbody>
</table>

**Table 2**: Endocrine changes before and after medication

<table>
<thead>
<tr>
<th>Group</th>
<th>FSH (U/L) Before drug use</th>
<th>FSH (U/L) After drug use</th>
<th>LH (U/L) Before drug use</th>
<th>LH (U/L) After drug use</th>
<th>E2 (pmol/L) Before drug use</th>
<th>E2 (pmol/L) After drug use</th>
<th>PRL (ng/ml) Before drug use</th>
<th>PRL (ng/ml) After drug use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mifepristone group</td>
<td>5.13±1.35</td>
<td>4.26±1.55</td>
<td>4.35±2.03</td>
<td>3.62±1.45</td>
<td>176.3±35.2</td>
<td>141.7±31.2</td>
<td>17.2±3.8</td>
<td>21.6±5.4</td>
</tr>
<tr>
<td>Gestrinone group</td>
<td>4.85±1.26</td>
<td>5.83±2.72</td>
<td>5.12±1.87</td>
<td>4.72±1.41</td>
<td>157.6±18.3</td>
<td>64.2±11.7</td>
<td>22.8±4.7</td>
<td>17.2±5.1</td>
</tr>
<tr>
<td>Control group</td>
<td>5.24±1.63</td>
<td>5.26±1.77</td>
<td>4.64±1.56</td>
<td>4.72±1.38</td>
<td>164.1±31.8</td>
<td>168.7±30.5</td>
<td>19.6±3.2</td>
<td>19.1±4.2</td>
</tr>
</tbody>
</table>

**Table 3**: Difference of CA125 before and after treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>Difference before and after treatment</th>
<th>F value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mifepristone group</td>
<td>60</td>
<td>22.5±1.8</td>
<td>8.13</td>
<td>0.00</td>
</tr>
<tr>
<td>Gestrinone group</td>
<td>60</td>
<td>15.4±1.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>60</td>
<td>12.1±1.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 4**: Comparison of two groups of symptom scores

<table>
<thead>
<tr>
<th>group</th>
<th>Observation time</th>
<th>Pelvic symptom score</th>
<th>Syndrome score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Dysmenorrhea</td>
<td>Coitus pain</td>
</tr>
<tr>
<td>Mifepristone group</td>
<td>Before treatment</td>
<td>7.12±1.52</td>
<td>6.83±1.34</td>
</tr>
<tr>
<td>Gestrinone group</td>
<td>After treatment</td>
<td>1.60±0.61</td>
<td>1.34±0.31</td>
</tr>
<tr>
<td>Control group</td>
<td>Before treatment</td>
<td>6.91±1.46</td>
<td>6.33±0.92</td>
</tr>
<tr>
<td>Mifepristone group</td>
<td>After treatment</td>
<td>2.26±0.84</td>
<td>1.70±0.64</td>
</tr>
<tr>
<td>Gestrinone group</td>
<td>Before treatment</td>
<td>6.83±1.33</td>
<td>6.04±1.44</td>
</tr>
<tr>
<td>After treatment</td>
<td>7.12±1.86</td>
<td>5.89±1.23</td>
<td>5.27±1.57</td>
</tr>
</tbody>
</table>

**Table 5**: Comparison of adverse reactions

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>Abnormal liver function</th>
<th>Gain weight</th>
<th>Acne</th>
<th>Hot flashes</th>
<th>Vaginal bleeding</th>
<th>Intimal thickening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mifepristone group</td>
<td>60</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Gestrinone group</td>
<td>60</td>
<td>17</td>
<td>11</td>
<td>11</td>
<td>40</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Control group</td>
<td>60</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

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treatment of endometriosis is effective. Gestrinone has strong anti progesterone and moderate anti estrogen, androgen and estrogen also has weak effect, can effectively promote the ectopic endometrial atrophy and absorption (Dindo et al., 2004). However, the long-term use of gestrinone can lead to elevated liver enzymes, androgen effect, and low levels of estrogen, and may also cause osteoporosis and increased blood ester (Emir et al., 2014). Mifepristone is a novel progesterone receptor antagonist, mifepristone has proved: Directly reduce estrogen and progesterone receptor content of endometrial function, and inhibit intimal interleukin secretion of -6 in immune regulation mechanism. Mifepristone can also alleviate the pain symptoms by inhibiting the production of prostaglandins (Goldstone et al., 2017).

Endometriosis can cause the micro environment of the patients with intra-abdominal change, combined with the hinder of the egg and sperm egg cell division and pick up the egg process are the main factors leading to female infertility (Koh et al., 2013). The anatomical structure of severe endometriosis can seriously damage the pelvic, uterus and rectum to cause adhesion and fallopian tube adhesion of uterus backward and pick up the egg function decline situation. In the past, laparoscopy is the first choice for severe endometriosis (Kertmen et al., 2015). It can effectively improve the pregnancy rate of patients after operation. However, the recurrence rate of endometriosis is very high. Although the laparoscopic operation can remove the ectopic focus of the naked eye, the atypical, small and deep focus of the invasive site, the close adhesion, the rupture and the complete lesion can not be removed, and the recurrence of the disease is caused by the effect of hormone after the operation (Liu et al., 2016). If the patient is given medication again after operation, the residual small lesions and naked eye lesions will be inhibited and atrophy and degeneration will occur.

Mifepristone is one of the progesterone receptor antagonists (Mukai et al., 2012). It has many aspects in the treatment of endometriosis. Mifepristone progesterone itself has no activity, but the combination of mifepristone and its receptor, the content of hypothalamus pituitary hormone receptor regulation system ER, PR, to block the endometrial response to estrogen, progesterone, progesterone inhibitory activity (Mellotte et al., 2015). In addition, mifepristone can also have a direct or indirect effect on the ovary, which affects the maturation and development of follicles, delays the ovulation period, induces the dissolution of the corpus luteum, and reduces the levels of progestin and estrogen in the patient's body, in favor of the treatment of endometriosis (Okada et al., 2011). Mifepristone can also directly affect endometrium endometrium, inhibit its increment and differentiation, promote its apoptosis and reduce its growth ability.

In addition, gestrinone can also act directly on the receptor in patients with endometriosis and ectopic endometrium of the endometrium and ectopic endometrial atrophy, so that the normal ovarian ovulation, improve the pregnancy rate (Carbonell et al., 2013). A lot of information, for severe endometriosis was treated with laparoscopic surgery after treatment; medication can significantly improve the clinical efficacy and pregnancy rate, and reduce the postoperative recurrence rate (Ono et al., 2009). Through this clinical treatment, the recurrence rate of mifepristone group and gestrinone group was significantly lower than that of the control group after treatment (Qi et al., 2015). The difference was statistically significant. The incidence of mifepristone and the incidence of liver function damage were significantly lower than that of the gestrinone group, and the difference was statistically significant. Thus, after laparoscopic surgery patients were given mifepristone can be effective in the treatment of severe endometriosis, alleviate the symptoms, the endometriosis lesions appeared atrophy, and no obvious adverse reactions. Although gestrinone is effective medicine for the treatment of severe endometriosis, can reduce the recurrence rate, but the damage of the drug on liver function is more serious and more adverse reactions, which should be paid attention to.

CONCLUSION

The results showed no significant difference between the two groups of curative effect of mifepristone and gestrinone, the operation will remove the ectopic lesions, combined with drug therapy after operation, can effectively control the symptoms and reduce the recurrence. Mifepristone and gestrinone for postoperative adjuvant therapy of endometriosis are safe and effective. The adverse reaction rate of mifepristone is low. In conclusion, mifepristone is a current research focus, its mechanism of action in the process of exploration, has broad prospects in the treatment of endometriosis, its long-term application security is paid more and more attention. Low dose treatment batch may be an effective solution, without affecting the treatment effect, can effectively reduce the adverse reaction caused by long-term medication.

REFERENCES


