Long Term and Low Dose Mifepristone in The Treatment of Uterine Leiomyoma

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Objective: To explore the long-term effect of low-dose mifepristone in the treatment of uterine leiomyoma. Methods: 90 cases of hysteromyoma treated in our hospital from December 2018 to May 2019 were randomly divided into control group and observation group, 45 cases in each group. The control group was treated with conventional dose (25mg / D) of mifepristone, and the observation group with low dose (12.5mg / D) of mifepristone. The uterine volume, uterine fibroid volume, hormone level, therapeutic effect and adverse reactions were compared between the two groups. Results: After treatment, the volume of uterus and hysteromyoma in the two groups decreased significantly, but there was no significant difference between the observation group and the control group (P > 0.05); the level of E2, P, FSH in the two groups decreased, but there was no significant difference between the observation group and the control group (P > 0.05); the treatment effect of the observation group and the control group was no significant difference (P > 0.05); the adverse reactions of nausea, anorexia, hot flashes and fatigue in the observation group The birth rate was significantly lower than that of the control group (P < 0.05). Conclusion: Low dose mifepristone can also effectively reduce the level of estrogen and progesterone in patients with uterine leiomyoma, reduce the volume of leiomyoma, reduce the incidence of adverse reactions, with high safety, which is worthy of clinical application.

Key words: Uterine fibroids; Small dose; Mifepristone; Efficacy
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Hysteromyoma is a relatively common benign tumor disease, which occurs in the middle-aged female population. Generally, there is no obvious clinical manifestation of the disease, and a few patients are accompanied with symptoms such as vaginal bleeding, compression and abdominal touching mass [1]. According to the relevant investigation, uterine fibroids are hormone dependent tumors, and the estrogen secreted by women can promote the growth of fibroids [2]. The etiology of women's uterine fibroids is more complex. At present, surgical treatment is mostly used in clinical treatment, but for the older patients with poor physical condition or large tumor volume, and the patients with more difficult surgical treatment need to carry out corresponding conservative treatment. The selection of appropriate drugs for effective conservative treatment is the focus of many medical researchers at present [3]. In drug therapy, mifepristone, with its strong progesterone antagonistic effect, is widely favored by clinicians and patients, but the use of different doses is still controversial [1]. Based on this, this study takes different doses of treatment for

patients with uterine leiomyoma. The purpose is to explore the therapeutic effect of low-dose mifepristone and provide reference for clinical medication. The report is as follows.

MATERIALS AND METHODS

General information

90 cases of hysteromyoma treated in our hospital from December 2018 to May 2019 were randomly divided into control group and observation group, 45 cases in each group. In the control group, the average age was (36.14 ± 5.47) years, the course of disease was 0.5-3 years, the average course of disease was (1.33 ± 0.86) years, 15 cases of intramural myoma, 12 cases of submucous myoma, 9 cases of subserosal myoma and 9 cases of multiple myoma. In the observation group, the age was 30-46 years, the average age was (37.53 ± 5.61) years; the course of disease was 0.6-3 years, the average course of disease was (1.45 ± 0.79) years; there were 14 intramural myomas, 13 submucosal myomas, 8 subserosal myomas and 10 multiple myomas. There was no significant difference between the two groups (P > 0.05).

Inclusion and exclusion criteria

Inclusion criteria: ①It was diagnosed as hysteromyoma after examination; ②It did not receive any hormone treatment in the past 1 month; ③The patients and their families all knew the basic information and signed the informed agreement. Exclusion criteria: ①History of allergy and contraindications; ②Malignant lesions in endometrium and cervix; ③Severe organ failure; ④Other serious infectious diseases and coagulation disorders; ⑤Serious mental diseases.

Method

Both groups took the same drug, mifepristone (produced by Shanghai Lizhu Pharmaceutical Co., Ltd., gjzz h20093852), the control group received routine dose (25mg / d) mifepristone treatment, the observation group received small dose (12.5mg / d) treatment, all took mifepristone every night before going to bed from the first day of menstruation, and continued to take the drug for 3 months. Before and after treatment, the patients underwent routine gynecological and pelvic examination, three-dimensional meridian or color ultrasound measurement of leiomyoma. During the treatment, the liver and kidney functions, blood and urine routine conditions were monitored on time every month, the level of estrogen and progesterone was monitored, and the patients were followed up for three months after treatment[16].

Observation indicators

①The volume changes of uterus and uterine leiomyoma before and after treatment were examined by B-ultrasound. ②The changes of hormone level in the two groups were detected, including estrogen (E2), serum FSH and progesterone (P). ③To evaluate the therapeutic effect of the two groups, which were divided into significant effect: the examination showed that the symptoms and leiomyoma of the patients disappeared, and the volume of the uterus returned to normal size; effective: after treatment, the symptoms were relieved or relieved, and the volume of the leiomyoma of the uterus reduced by more than 20%; ineffective: after treatment, the symptoms did not change compared with before treatment, and the condition of the serious patients worsened. Total effective rate = significant efficiency + effective rate. ④Adverse reactions were recorded in the two groups, including nausea, anorexia, hot flashes, fatigue, etc.

Statistical methods

Using SPSS 21.0 statistical software, "mean ± standard deviation" means measurement data, with t-test; counting data is made up of%, with x^2 test, P < 0.05 is statistically significant.

RESULTS

Comparison of the volume changes of uterus and hysteromyoma before and after treatment

Before the treatment, there was no significant difference in the volume of uterus and uterine fibroids between the two groups (P > 0.05); after the treatment, the volume of uterus and uterine fibroids in the two groups were significantly reduced, and there was no significant difference between the observation group and the control group (P > 0.05), as shown in Table 1.

Table 1.
Comparison of the volume changes of uterus and hysteromyoma between the two groups before and after treatment ($\bar{x} \pm s$)

Group	Number of cases	Uterus volume (cm^3)		Uterine fibroid volume (cm^3)	
		Before treatment	After treatment	Before treatment	After treatment
Control group	45	155.25±11.36	85.60±6.19	218.46±18.50	97.30±10.20
Observation group	45	156.45±12.17	86.59±6.13	217.96±17.73	96.20±10.42
t	-	0.483	0.762	0.130	0.966
P	-	0.629	0.447	0.896	0.336

Comparison of hormone levels

Before treatment, there was no significant difference in E_2, P and FSH levels between the two groups (P > 0.05); after treatment, E_2, P and FSH levels decreased, and there was no significant difference between the observation group and the control group (P > 0.05), as shown in Table 2.

Table 2.
Comparison of hormone levels between the two groups ($\bar{x} \pm s$)

Group	Number of cases	E_2 (pmol/L)		P (nmol/L)		FSH (U/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	45	285.5±26	160.2±16	8.41±1.8	3.45±1.5	9.1±3.2	7.56±2.4
Observation group	45	286.1±25	158.3±15	8.24±1.5	3.24±0.8	8.9±2.9	7.21±2.2
t	-	0.111	0.639	0.486	0.828	0.317	0.721
P	-	0.911	0.457	0.627	0.409	0.756	0.472

Treatment effect comparison

There was no significant difference between the observation group and the control group (P > 0.05), as shown in Table 3.

Table 3.
Comparison of therapeutic effect between the two groups [n (%)]

Group	Number of cases	Markedly effective	Effective	Invalid	Total effective rate
Control group	45	27（60.00）	15（33.33）	3（6.67）	42（93.33）
Observation group	45	29（64.44）	14（31.11）	2（4.44）	43（95.56）
X^2	-	-	-	-	0.473
P	-	-	-	-	0.491

Comparison of adverse reactions

The incidence of nausea, anorexia, hot flashes and fatigue in the observation group was significantly lower than that in the control group (P < 0.05), as shown in Table 4.

Table 4.
Comparison of adverse reactions between the two groups [n (%)]

Group	Number of cases	Nausea	Weak	Anorexia	Hot flashes	Total incidence rate
Control group	45	3（6.67）	3（6.67）	2（4.44）	2（4.44）	10（22.22）
Observation group	45	1（2.22）	1（2.22）	1（2.22）	1（2.22）	4（8.89）
X^2	-	-	-	-	-	6.763
P	-	-	-	-	-	0.009

DISCUSSION

Uterine fibroids are the most common benign tumors in female reproductive organs. The pathogenesis of uterine fibroids is still unclear, probably due to mutations in normal myometrial cells, more complex interactions between sex hormones and local growth factors [4]. According to a large number of clinical studies, uterine fibroids are highly dependent on hormones. Estrogen is the main cause of fibroid growth. In addition, ovarian function and hormone metabolism are regulated and controlled by nerve centers. Central activities may also have an important impact on the onset of fibroids [5]. Some patients with uterine fibroids have

clinical symptoms such as constipation, increased menstrual flow, and pelvic mass, which have a serious impact on the quality of life of patients. At present, the clinical treatment of this disease is often treated with surgical resection. Because the pathogenesis and development direction of the disease is still unclear, it has caused certain difficulties in the treatment of the disease. According to relevant medical data, pregnant women are often accompanied by uterine fibroids, and women have a strong secretion of female hormones during pregnancy. Uterine fibroids grow rapidly during this period, occupying a large area of the uterus, fibroids may also cause pelvic infection or suppuration, if the uterine horn fibroids oppress the fallopian tube, leading to uterine deformation, there is a high probability of miscarriage, Symptoms such as premature birth may pose a threat to the life of the fetus and pregnant women [6]. In addition, excessive consumption of high-fat foods, excessive body weight, long-term use of hormonal drugs and health products, and use of estrogen-containing cosmetics may cause small doses of estrogen to accumulate in the body, irregular diet, and post-pregnancy sexual life. Sexual life disorders, unclean sex life, and irregular contraceptive measures are all high-risk factors that induce uterine fibroids [7].

In this study, the results of mifepristone treatment for patients with uterine fibroids showed that after treatment, the uterus volume and uterine fibroid volume were significantly reduced in the two groups, and there was no significant difference between the observation group and the control group (P>0.05), indicating that mifepristone is effective in the treatment of uterine fibroids, and both low-dose and conventional doses of mifepristone achieve therapeutic goals. Analysis of the reasons, mifepristone as a strong anti-progesterone, can effectively bind to the progesterone receptor and glucocorticoid receptor, the drug has a very high affinity with the endometrial progesterone receptor, can be used as An anti-early pregnancy drug [8]. After entering the human body, the drug can directly bind to the glucocorticoids in the hypothalamus and ovaries, thereby reducing the levels of estrogen and progesterone in the body. Mifepristone can slow the movement of endometrial glands and block the blood supply of uterine fibroids, thus affecting their growth and development [9]. Uterine fibroids have no blood supply and will soon weaken or die. The study found that after taking mifepristone, the levels of E2, P and FSH in both groups decreased, which proved that the drug can reduce the levels of estrogen and progesterone, thereby inhibiting ovulation and amenorrhea. [10, 11]. The drug quickly works within 0.81~1.5 hours after oral administration, and the blood peak is 0.8mg/L and 2.34mg/L, but it is affected by individual differences, and the elimination rate is slow in the body, usually 20~34 hours. Within 72 hours after taking the drug, the concentration of blood drug can still be maintained at about 0.2mg/L. The drug can significantly improve the sensitivity of the uterus to prostaglandins. The use of a small amount of mifepristone combined with prostaglandins can effectively terminate. Early pregnancy [6]. In addition, mifepristone is a synthetic steroid with strong progesterone antagonism and weak glucocorticoid antagonism, which can inhibit hypothalamic glandular axis through non-competitive anti-stimulatory action, leading to atrophy of uterine fibroids. Can be better combined with progesterone receptors. There is another reason for the reduction of uterine fibroids. Mifepristone can reduce arterial blood flow and increase blood flow resistance, resulting in the reduction of uterine fibroids [12, 13]. In this experiment, the patients in the observation group were treated with low-dose mifepristone, and the control group was treated with conventional dose. The uterine fibroids in the two groups were effectively improved, but the difference in treatment effect between the two groups was still observed. After treatment, the uterus and uterine fibroids were smaller than the control group, and the probability of adverse reactions during the treatment group was significantly lower than that of the control group (P<0.05).

Zhou Mianli, Mao Hui [14], etc. In the study of the efficacy of GuizhiFuling Capsule combined with mifepristone in the treatment of uterine fibroids and the effects of serum VEGF, ER and

PR levels, 72 patients with uterine fibroids were divided into control group. In the observation group, Guizhi and Guizhifu capsules were combined with mifepristone to conclude that the observation group has a more effective treatment effect, which greatly reduces the volume of uterus and uterine fibroids, and can effectively reduce serum VEGF, ER and The PR level and the incidence of adverse reactions in the observation group were significantly lower than those in the control group. It is proved that mifepristone is effective in the treatment of uterine fibroids and can be combined with other drugs to further improve the therapeutic effect. Liu Jianzhong, Zhang Chunhua[15] and other patients in the treatment of uterine fibroids with different doses of mifepristone in the effect and serological study, patients with uterine fibroids were treated with conventional and low-dose mifepristone, and concluded: low dose Mifepristone is more effective, with lower levels of related hormones and better clinical control. Although the above scholars' research methods are different from this study, the conclusions are consistent, which can confirm the accuracy of this study.

CONCLUSION

In summary, the use of low-dose mifepristone in the treatment of uterine fibroids can also effectively reduce the level of estrogen and progesterone, reduce the volume of fibroids, reduce the incidence of adverse reactions, and have high safety, which is worthy of clinical application.

REFERENCES

1. Tao Xuefeng LY, Wang Yaqin, et al. The efficacy of Guizhi Fuling Pill combined with mifepristone in the treatment of uterine fibroids and its effects on serum progesterone receptor, estrogen receptor and vascular endothelial growth factor Drug Evaluation Research. 2018;36(4):607-610.
2. Zhang Limin LF, Liu Haiying, et al. Therapeutic effect of mifepristone combined with Guizhi Fuling Pill in the treatment of uterine fibroids. Chinese Journal of Clinical Oncology and Rehabilitation. 2017;19(1):36-38.
3. Islam MS, Ciavattini A, Petraglia F, Castellucci M, Ciarmela P. Extracellular matrix in uterine leiomyoma pathogenesis: a potential target for future therapeutics. Human Reproduction Update. 2017;24(1):59-85. doi:https://doi.org/10.1093/humupd/dmx032
4. Gao Yanmin SX, Liu Lianchen, et al. Effects of low-dose mifepristone on estrogen and progesterone levels, uterus and tumor volume in patients with uterine fibroids. Laboratory Medicine and Clinic. 2017;14(20):3058-3060.
5. Fu Jianhua YY, Wang Bo, et al. Application of mifepristone in the treatment of uterine fibroids and its effect on postoperative recurrence. Chinese Journal of Preventive Medicine. 2018;36(07):66-68.
6. Wei S. Effect of Guizhi Fuling Pill combined with mifepristone in the treatment of uterine fibroids and its effect on serum sex hormones and ER, VEGF, IL-2 levels Chinese Maternal and Child Health Care. 2018;33(5):1013-1015.
7. Liu C, Lu Q, Qu H, et al. Different dosages of mifepristone versus enantone to treat uterine fibroids: A multicenter randomized controlled trial. Medicine (Baltimore). 2017;96(7):e6124-e6124. doi:https://dx.doi.org/10.1097%2FMD.0000000000006124
8. Yu Canyang ZH, Huang Jianmei. Correlation between VEGF and MVD in uterine fibroids and mechanism of mifepristone in the treatment of uterine fibroids. Journal of Practical Cancer. 2018;33(1):30-32.
9. Shen Q, Shu L, Luo H, Hu X, Zhu X. The use of mifepristone in abortion associated with an increased risk of uterine leiomyomas. Medicine (Baltimore). 2017;96(17):e6680-e6680. doi:https://dx.doi.org/10.1097%2FMD.0000000000006680
10. Ling Y. Comparison of clinical efficacy and recurrence rate of laparoscopic myomectomy combined with triptorelin or mifepristone in the treatment of multiple uterine fibroids. Chinese Maternal and Child Health Care. 2019;34(08):1897-1899.
11. Zhang Y, Wang J, Zuo C, et al. Protective Effect of Taohong Siwu Decoction on Abnormal Uterine Bleeding Induced by Incomplete Medical Abortion in Rats during Early Pregnancy. Chemical and Pharmaceutical Bulletin. 2018;66(7):708-713. doi:https://doi.org/10.1248/cpb.c17-00945
12. Wen Yuling WS. Effects of mifepristone on the levels of SOCS-3, Bcl-2, Bax and caspase-3 in patients with endometriosis. Journal of Medical Molecular Biology. 2018;15(5):348-351.
13. Sant'Anna GdS, Brum IS, Branchini G, Pizzolato LS, Capp E, Corleta HvE. Ovarian steroid hormones modulate the expression of progesterone receptors and histone acetylation patterns in uterine leiomyoma cells. Gynecological Endocrinology. 2017/08/03 2017;33(8):629-633. doi:https://doi.org/10.1080/09513590.2017.1301924
14. Zhou Mianli MH, Yu Xiaolan, et al. Effect of Guizhi Fuling Capsule combined with mifepristone on uterine fibroids and its effect on serum VEGF, ER and PR levels. Chinese Journal of Clinical Oncology and Rehabilitation. 2017;18(8):81-84.
15. Liu Jianzhong ZC, Liu Tingting. Effect and serological study of different doses of mifepristone in the treatment of uterine fibroids. Chinese Maternal and Child Health Care. 2019;34(01):36-38.
16. Nahla O. Mousa1, 2 , Marwa Gado1 AO. Multimodality of Human Epidermal Growth Factor Receptor-2 Antagonism Restores the Apoptotic Capacity of Liver Cancer Cells. J Nat Sci Biol Med. 2020;11(2):118-133. doi:10.4103/jnsbm.JNSBM