Effect of laparoscopy combined with mifepristone in the treatment of endometriosis and drug reaction analysis

Jing Li*, Huilin Yang and Jie Song**
Obstetrics Department, Yidu Central Hospital of Weifang, Qingzhou, Shandong, China

Abstract: Endometriosis is a common benign disease of Gynecology, which often causes symptoms of dysmenorrhea, pelvic pain and infertility. In this paper, we analyzed the effect of laparoscopy combined with mifepristone in the treatment of endometriosis. By observing the clinical efficacy and side effects of small dose mifepristone, we explored the feasibility of small dose mifepristone in the treatment of recurrent endometriosis. The results showed that the clinical symptoms of small dose mifepristone group and danazol group were improved to varying degrees. The improvement rate of mifepristone group was 96.7% for dysmenorrhea and 61.1% for non menstrual lower abdominal pain, respectively. In conclusion, small dose mifepristone is an effective treatment for recurrent endometriosis with high remission and good curative effect.

Keywords: Mifepristone, endometriosis, danazol, drug effect, side effect, clinical research.

INTRODUCTION

Endometriosis (EM) is a common benign disease in gynecology, but it has the characteristics of plant growth and distant metastasis. The incidence of women with childbearing age is about 10% (Mannen *et al.,* 2010; Galasso *et al.,* 2015). The incidence of infertility is 30% to 60% (Sanomura *et al.,* 2014; Luo, 2015). The disease often causes symptoms such as dysmenorrhea, pelvic pain and infertility. In recent years, the incidence of this disease is rising because of the more and more extensive application of diagnostic laparoscopy (Trzeciak *et al.,* 2016). Endometriosis and endometrial tissue are invasive and progressive, and their pathological process is gradual (Khera *et al.,* 2015). Although surgical treatment is not successful, there is a possibility of recurrence. The recurrence rate of conservative surgery in 5 years was 20%-40% (Singh *et al.,* 2016). The recurrence of endometriosis is the recurrence of the original symptoms and signs after a few months after a successful drug or surgical treatment (Vagnarelli *et al.,* 2015). The treatment of recurrent endometriosis includes conservative surgery, radical or radical surgery and drug treatment (Josep *et al.,* 2016; Claudia *et al.,* 2017). Due to China's economic conditions, people's traditional concept of bondage and people pay more attention to the quality of life and other factors, many patients to accept again surgery or radical surgery (Wang, 2013), often require drug treatment, so to seek an effective drug for the treatment of recurrent endometriosis is a pressing matter of the moment.

At present, there is a lack of research on the treatment of recurrent endometriosis (Galasso *et al.,* 2015). Therefore, a small dose of mifepristone is used in the treatment of recurrent endometriosis after conservative surgery, as the experience group (Bedaiwy *et al.,* 2017). At the same time, the drug treated with danazol was the control group. By observing the clinical efficacy, side effects and the effects of mifepristone on blood estradiol, cortisol and lipid metabolism, we discussed the feasibility of low-dose mifepristone in the treatment of recurrent endometriosis.

MATERIALS AND METHODS

Research object

A total of 142 patients who were diagnosed with endometriosis recurrence in our hospital in 2016 were selected. All patients were approved by Ethics Committee of our hospital and signed on the informed consent, ethics committee number as 16XSFGT-B. Inclusion criteria: Endometriosis patients who had undergone laparotomy or laparoscopy for the treatment of endometriosis were reappearance of dysmenorrhea, or non - menstrual abdominal pain, and other clinical manifestations. In pelvic examination, there were palpable nodules or inactive cystic masses beside the uterus. B ultrasonography was consistent with the signs of endometriosis. Within the first 3 months of the study, no drug or surgical treatment for endometriosis had been received. The function of liver and kidney and the normal blood cortisol were normal. No heart disease, liver disease, kidney disease, endocrine disease and so on.

Grouping and drug delivery

Mifepristone in the treatment group of 78 people, 22~48 years of age, the average age of 35.8±5.2 years; the average weight of 51.2±8.6kg; and 64 people in the davazolazole group, aged 21~48 years, with an average age of 36.2±6.7 years, with an average weight of 52.6± 9.1kg. There were no statistical differences in age, weight, course of disease, diagnosis and disease staging in the two groups.

**Corresponding author:* e-mail: qzbzwb@163.com

**Jing Li and Huilin Yang contributed equally to this work.

Mifepristone group was used 1 mifepristone daily, with a daily dose of 10mg and the first day of menstruation for 84 days. The control group took danazol 2 tablets each time, 2 times a day, the total daily dose of 400mg, 84 days of continuous use after the first day of menstruation.

Observation index

The symptoms of dysmenorrhea, non-menstrual hypogastric pain, and pain symptoms were observed before and after the symptoms were observed. The subjective symptoms were divided into 4 levels according to the severity of each symptom. 0=has no pain symptoms, 1= is mild (pain tolerable, normal life is not affected), 2=is moderate (pain is tolerable, but medication is required, normal life is not affected), 3= is severe (severe pain, intolerable, and pain killers must be used, and sleep is seriously affected). Any improvement or disappearance of pain in dysmenorrhea and non menstrual hypogastric pain is the improvement of symptoms.

The number of improved cases of concave nodules, pelvic pain, and limited uterine activity was observed before and after the use of drugs. Standard of uterine activity limitation 0= activity was normal; 1= was mild limited; 2= was moderately limited; 3= was inactive. The obvious reduction and disappearance of the painful nodules of the posterior dome, or the obvious reduction or disappearance of the nodule touch were all seen as the improvement of the signs. The same physician was responsible for the examination before and after the drug use.

Liver function tests were performed on the first visit, medication for 1 month, medication for 2 months and after 3 months of medication. The changes of liver function caused by two groups of drugs were observed so that the side effects were treated in time. The subjects were treated with the first diagnosis and the blood lipid examination after 3 months of medication. The changes of total cholesterol, low density lipoprotein and high density lipoprotein (HDL) before and after the two groups were recorded, and the effects of the two groups on the metabolism of blood lipid were observed before and after the use of the drugs.

STATISTICAL ANALYSIS

The results were all expressed in X±s and the count data were statistically treated by X^2 test and the measurement data were statistically treated with t-test.

RESULTS

Improvement of symptoms and signs

Most of the 142 patients had amenorrhea after 1 month of medication. The clinical symptoms of small dose mifepristone group (experimental group) and davalazol group (control group) were improved to varying degrees. The improvement rate of mifepristone group and dacazole group on dysmenorrhea was 96.7% and 94.5% and the improvement rate of abdominal pain in non menstrual period was 61.1% and 77.2%, respectively.

The improvement rate of pelvic tenderness was 83.33% and 84.8% respectively, and the improvement rate of posterior tubercle was 75% and 77.2%, respectively. The improvement rate of uterine movement limitation was 70.5% and 74.2%, respectively. There was no significant difference in the improvement rate of symptoms and signs between the two groups (P>0.05), as shown in table 1, table 2. The volume improvement rate of small ovarian ectopic cysts in the two groups was 66.67% 72.22% after small dose of mifepristone and datrazole. There was no significant difference in x2 test (P>0.05). See table 3.

Ovarian function

There was no significant difference in serum E2 between the two groups before treatment (p>0.05). After treatment, the serum E2 values of the two groups were lower than those before the treatment, and the E2 values of the serum were significantly different between the two groups before and after treatment (P<0.01). There were also significant differences between the groups after treatment (P<0.01). After treatment with small dose of mifepristone group E2 as 65.3±21.6pg/ml in the follicular phase, danazol group was 25.8±4.1pg/ml in AMP level after menopause. See table 4. The average thickness of endometrium in the two groups decreased, and there was no significant difference between the two groups after treatment with t test (p>0.05) (table 5).

There was no significant difference between the two groups before and after treatment of total cholesterol, low density lipoprotein and high density lipoprotein (P> 0.05). See table 6. The main side effects were hot flashes, irregular vaginal bleeding, weight gain, ALT abnormalities, gastrointestinal reaction and acne. The weight gain and the incidence of acne in the small dose mifepristone group were significantly lower than that of the davazolazole group, and the statistical difference was significant (P<0.01) (table 7).

DISCUSSION

The biological basis of EM recurrence is that ectopic endometrium cells can survive and have hormone maintenance (Akhter *et al.,* 2009). The results showed that the ectopic foci in the mice were induced by operation, and the GnRH-a was treated for 42 days and the ectopic foci were atrophied and atrophied in the treatment (Cahill *et al.,* 2015). However, the inhibitory state could be recovered after 3 weeks of drug treatment or 3 weeks after the use of steroid hormone replacement therapy. In the laparoscopic resection of ovarian ectopic foci, and progesterone or goserelin treatment for 6 months,

Table 1: Changes of symptoms before and after treat

Group	Dysmenorrhea			Non menstrual hypogastric pain		
	Before treatment	After drug use	Rate of improvement %	Before treatment	After drug use	Rate of improvement %
Experience group	62	2	96.7%	18	7	61.1%
Control group	37	2	94.5%	22	5	77.2%

Table 2: Changes of physical signs

Group	Pelvic pain			Trapping concave nodule			Restriction of uterine activity		
	Before treatment	After drug use	Rate of impr. %	Before treatment	After drug use	Rate of impr. %	Before treatment	After drug use	Rate of impr. %
Experience group	42	7	83.3%	52	13	75.0%	17	5	70.5%
Control group	33	5	84.8%	44	10	77.2%	31	8	74.2%

Table 3: Volume improvement of ovarian ectopic cysts after drug use

Group	Improved number	Not improved	number before the treatment	Rate of improvement%
Experience group	17	11	28	60.7
Control group	12	7	19	63.1

Table 4: Changes of serum E2

Time	Experience group	Control group	P value
Before treatment	98.2±17.5	99.7±15.2	P>0.05
After treatment	65.3±21.6	25.8±4.1	P<0.01
P value	P<0.01	P<0.01	

Table 5: Endometrium thickness

Time	Experience group	Control group	P value
Before treatment	0.62±0.14	0.71±0.21	P>0.05
After treatment	0.53±0.17	0.60±0.13	P>0.05
P value	P>0.05	P<0.01	

Table 6: Influence of blood lipid metabolism

Type	Experience group			Control group		
	Before treatment	After drug use	P value	Before treatment	After drug use	P value
total cholesterol	4.21±0.83	4.15±0.77	P>0.05	4.15±0.79	3.98±0.64	P>0.05
Low density lipoprotein	2.36±0.79	2.28±0.72	P>0.05	2.48±0.58	2.72±0.43	P>0.05
High density lipoprotein	1.47±0.19	1.36±0.23	P>0.05	1.12±0.25	1.23±0.31	P>0.05

Table 7: Side effects after medication (number of cases)

Group	Vaginal bleeding	Gain weight	ALT anomaly	Changes of gastrointestinal function	Acne	Hot flashes
Experience group	17	9	3	11	5	25
Control group	15	42	5	7	12	21

histologic findings in some residual foci, nuclear fission is still very active, not degenerating phenomenon (Caziuc *et al.,* 2015). It may be associated with fibrous encapsulation around the lesion and impeding the entry of drugs into the cell (Jia *et al.,* 2015). In addition, the concentrations of ER and PR in ectopic endometrium were significantly lower than those in eutopic endometrium (Dobson *et al.,* 2015; Ghoneum *et al.,* 2015). The low concentrations of

ER and PR in ectopic endometrium may be the reasons for the poor response of ectopic endometrium to hormone therapy. Recurrent endometriosis is a recurrence of the original symptoms and signs after a few months after a successful drug or surgical treatment (Fang *et al.,* 2017). The main manifestation of recurrence is pain and nodules or lumps. 80% can be seen in pelvic examination, but ultrasound scanning and serum CA125 can help. The most accurate recurrence diagnosis is laparoscopy (Espinel *et al.,* 2015).

The correlation between the severity of EM and the recurrence is still controversial. There were reports of laparoscopy in EM patients and found that the severity of EM and the AFS score did not predict the recurrence of EM (Hess *et al.,* 2016). But the involvement of the lesion is completely removed and the possibility of recurrence is very small, so it is considered that the recurrence of EM is not related to the severity of the disease, but it is related to the surgical completeness (Kawamoto *et al.,* 2016). The formation of pelvic endometriosis is related to the function of the ovary (Galasso *et al.,* 2015). The non physiological recurrent bleeding of ectopic implantation is ovarian steroid hormone dependent process. The recurrence rate of ovarian endometriosis is significantly reduced. Whether or not the ovary is excised at the same time during total hysterectomy for endometriosis can affect the recurrence rate after the operation. The relative risk of recurrent pain in the ovaries was 6.1 and the relative risk for the reoperation of the ovaries was 8.1 (Khera *et al.,* 2015).

Mifepristone *in vivo* competition combined with progesterone receptor, and has a strong anti progestin effect. The affinity of mifepristone to PR is 5 times higher than that of progesterone (Luo, 2015). Among them, the affinity between the de methylated derivative and PR is the highest, and the binding protein receptor two Mer is formed by competitive binding of endogenous PR to inhibit the transcriptional activity of the gene. It is well known that the onset and recurrence of endometriosis are related to the periodic changes in the ovary (Mannen *et al.,* 2010; Galasso *et al.,* 2015). At present, various methods are considered to reduce hormone levels in the body to achieve amenorrhea and ectopic endometrium atrophy, which is an effective treatment for recurrent endometriosis. Mifepristone is an anti progesterone drug acting on the receptor level. It blocks the progesterone by binding with the receptor, thereby inhibiting ovarian function, inducing amenorrhea, and making the ectopic endometrium atrophy (Hess *et al.,* 2016). Mifepristone acts on the hypothalamus pituitary ovary axis. It not only inhibits the secretion of LHRH in the hypothalamus, but also directly acts on the pituitary gland, inhibits the secretion of FSH and LH, and then inhibits the secretion of progesterone (Fang *et al.,* 2017). Mifepristone can also enhance the phagocytic activity of peritoneal macrophages. In vitro experiments also showed that mifepristone directly reduced the contents of estrogen and progesterone receptors in endometrium and participated in immune regulation by decreasing the secretion of interleukin 6.

CONCLUSION

The symptoms of dysmenorrhea and pelvic pain caused by endometriosis are chronic and persistent, and the clinical treatment is often long-term. Therefore, the clinical work must consider the drug efficacy, safety, patient tolerance and treatment costs, compliance and so on to choose the treatment plan. Mifepristone has the advantages of convenient drug use and small economic burden. The main side reaction of mifepristone was the response to glucocorticoid and the major side effects of dadazol were ovarian inhibition and androgen assimilation. In conclusion, small doses of mifepristone in the treatment of recurrent endometriosis have high relief, good curative effect, convenience, low price, less side effects and less adverse reactions. The efficacy and safety of mifepristone in the treatment of recurrent endometriosis still lack a clinical study of large cases. Previous studies have not been followed for a long time. In future, we need to expand clinical case study and extend follow-up time, and further observe the long-term efficacy and safety of mifepristone in the treatment of recurrent endometriosis.

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REFERENCES

Akhter N and Milford-Beland S (2009). Gender differences among patients with acute coronary syndromes undergoing percutaneous coronary intervention in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). *Am. Heart J.*, **157**(1): 141-148.

Bedaiwy M, Alfaraj S, Yong P and Casper R (2017). New developments in the medical treatment of endometriosis. *Fertility and Sterility*, **107**: 12-15.

Claudia T, Antonella B, Giuseppe M, Giuseppe B, Stefano L and Felice P (2017). Hormonal therapy for endometriosis: From molecular research to bedside. *Euro. J. Obst. & Gyne. Repro. Biol.,* **209**: 61-66.

Cahill G, Tran L, Baker RA, Brown A, Huang YC and Ou CW (2015). Principles of radiation oncology. *Medical Journal,* **1**(01): 27-38.

Caziuc A, Calin Dindelegan G, Pall E and Mironiuc A (2015). Stem cells improve the quality of colonic

anastomoses - A systematic review. *J. Buon.,* **20**(6): 1624-1629.

Dobson PR, Brown BL, Beck D, Yang H, Zhou J and Voon YL (2015). Management of surgical oncologic emergencies. *Asian Pac. J. Surg Oncol*., **1**(02): 59-72.

Espinel J, Pinedo E, Ojeda V and Del and Rio MG (2015). Treatment modalities for early gastric cancer. *World J. Gastrointest. Endosc.*, **7**(12): 1062-1069.

Fang W and Ruan W (2017). Advances in uniportal video-assisted thoracoscopic surgery for non-small cell lung cancer. *Minim Invasive Surg Oncol.*, **1**(1): 20-30.

Ghoneum M, Felo N, Nwaogu OM, Fayanju IY, Jeffe JA and Margenthaler DB (2015). Clinical Trials in Surgical Oncology. *Asian Pac. J. Surg Oncol*., **1**(02): 73-82.

Hess PL and Wojdyla DM (2016). Sudden Cardiac Death After Non-ST-Segment Elevation Acute Coronary Syndrome. *JAMA. Cardiol*., **1**(1): 73-79.

Galasso G, Savonitto S and Piccolo R (2015). Effect of an invasive strategy on outcome in patients ≥75 years of age with non-ST-elevation acute coronary syndrome. *Am. J. Cardiol.*, **115**(5): 576-580.

Josep L, Ana M, Yara L, Jesús G and Braulio H (2016). Mifepristone 2.5, 5, 10mg versus placebo in the treatment of endometriosis, *J. Repro. Heal. Med.*, **2**(1): 17-25.

Jia WZ, Zhao JC, Sun XL and Yao Z (2015). Additive anticancer effects of chrysin and low dose cisplatin in human malignant glioma cell (U87) proliferation and evaluation of the mechanistic pathway. *J. Buon.*, **20**(5): 1327-1336.

Kawamoto KR, Davis MB and Duvernoy CS (2016). Acute Coronary Syndromes: Differences in Men and Women. *Curr. Atheroscler. Rep.*, **18**(12):73.

Khera S, Kolte D and Gupta T (2015). Temporal Trends and Sex Differences in Revascularization and Outcomes of ST-Segment Elevation Myocardial Infarction in Younger Adults in the United States. *J. Am. Coll. Cardiol*., **66**(18): 1961-72.

Luo Xuejian (2015).Clinical research of azithromycin in treatment of acute enteritis. *Guangzhou Medical Journal*, **22** (03): 80-81.

Mannen K, Tsunada S and Hara M (2010). Risk factors for complications of endoscopic submucosal dissection in gastric tumors: Analysis of 478 lesions. *J Gastroenterol*, **45**(1): 30-36.

Sanomura Y, Oka S and Tanaka S (2014). Continued use of low-dose aspirin does not increase the risk of bleeding during or after endoscopic sbmucosal dissection for early cancer. *Gastric Cancer,* **17**(3): 489-496.

Singh DP, Singh SS, Singh S, Shrivastava AK and Sinha K (2016). Clinical profile of acute coronary syndrome (ACS) in young adults of North Indian population. *J. Assoc. Physicians India*, **64**(1): 33.

Trzeciak P and Wożakowska-Kapłon B (2016). Comparison of Inhospital and 12- and 36-Month Outcomes After Acute Coronary Syndrome in Men Versus Women <40 Years (from the PL-ACS Registry). *Am. J. Cardiol*., **118**(9): 1300-1305.

Vagnarelli F, Taglieri N and Ortolani P (2015). Long-term outcomes and causes of death after acute coronary syndrome in patients in the Bologna, Italy, area. *Am. J. Cardiol.,* **115**(2): 171-177.

Wang X (2013). Clinical efficacy and analysis of azithromycin in treatment of acute enteritis. *Gui. Chin. Medi.*, **21**(29): 423-424.