

Efficacy of mifepristone plus Shenqi Yangxue Granules for hysteromyoma complicated with anemia and its effect on hemoglobin, erythrocytes and hematocrit

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Abstract: To assess the clinical efficacy of mifepristone complicated with anemia and its effect on the hemoglobin, red blood cell, as well as hematocrit. Sixty patients with hysteromyoma complicated with anemia between December 2018 and December 2020 were recruited and assigned to receive either mifepristone (control group, n=30) or mifepristone plus Shenqi Yangxue Granules (experimental group, n=30) based on the admission order. The two groups were compared in clinical efficiency, incidence of adverse reactions, myoma volume, uterine volume, and clinical indicators. The experimental group got a notably higher total treatment efficiency than the control group ($P<0.05$). The experimental group obtained a remarkably lower incidence of adverse reactions and smaller myoma volume and uterine volume than the control group ($P<0.05$). Patients in the experimental group showed lower hemoglobin levels and higher hematocrit levels than the control group ($P<0.05$). Combined therapy of mifepristone plus Shenqi Yangxue Granules resulted in lower erythrocyte aggregation index, erythrocyte sedimentation rate, in patients in the study group than those receiving mifepristone alone in the control group ($P<0.05$). Mifepristone plus Shenqi Yangxue Granules for patients with hysteromyoma complicated with anemia mitigates the clinical symptoms of patients and reduces the incidence of adverse reactions, with a high safety profile.

Keywords: Mifepristone, Shenqi Yangxue Granules, hysteromyoma with anemia, blood picture.

INTRODUCTION

Hysteromyoma is a benign tumour caused by the abnormal proliferation of smooth muscle cells in the uterus. The early symptoms of the disease are insidious, and the clinical symptoms in the advanced stage include severe anemia, pelvic compression, abnormal menstruation, abdominal masses, and abnormal uterine bleeding, which compromises the daily life and health safety of patients (Check *et al.*, 2021; Landis *et al.*, 2021; Luo *et al.*, 2021). Currently, surgery is the treatment of choice for patients with hysteromyoma complicated with anemia. However, surgical treatment is traumatic and prone to complications, which may impair the reproductive function, so a portion of patients seeks treatment with recourse to conservative medication. In addition, surgical treatment fails to cure the anemia despite its effectiveness in hemostasis and predisposes the patients to impaired body immunity in severe cases, resulting in postoperative infections and prolonged postoperative recovery. Mifepristone antagonizes progesterone receptors and inhibits the growth of uterine smooth muscle cells, thereby effectively reducing the size of the myoma and relieving the patient's symptoms. Nevertheless, long-term administration of mifepristone may disturb the menstrual cycle of patients and lead to drug dependence (Allanson *et al.*, 2021; Gubbi *et al.*, 2021; Landis *et al.*, 2021; Yan *et al.*, 2020). Relevant

studies have shown that the Shenqi Yangxue Granules is a tonic for anemia with the effect of tonifying the kidney, strengthening the spleen, producing blood and replenishing energy. Accordingly, the current study was conducted to investigate the clinical efficacy of mifepristone plus Shenqi Yangxue Granules for hysteromyoma complicated with anemia and its effect on the hemoglobin (HB), red blood cell (RBC), and hematocrit (HCT).

MATERIALS AND METHODS

General data

In this study, 60 patients with hysteromyoma complicated with anemia between December 2018 and December 2020 were recruited and randomized into experimental and control groups based on the order of admission, with 30 cases in each group. This study was approved by the ethics committee of Tianchang Hospital of traditional Chinese Medicine and the ethics approval number is 2018-11-15.

Inclusion criteria

Patients who met the diagnostic criteria of hysteromyoma and were clinically diagnosed with anemia, with complete general information, with excessive menstruation, with the maximum diameter of a single tumour body of <4 cm, and who provided written informed consent were included.

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Exclusion criteria

Patients with hematological system diseases, with liver or kidney dysfunction, or coagulation dysfunction, with other causes of anemia, with serious bacterial infections and viral infections, in pregnancy or lactation, with allergies to the drugs applied in this study and with psychiatric diseases were excluded.

Methods

The control group received 0.5mg of mifepristone (Approval No. H10950202; Shanghai Xinhualian Pharmaceutical Co., Ltd.) daily for 6 weeks. A similar administration regimen of mifepristone was introduced to the patients in the experimental group.

The experimental group also received 1g of Shenqi Yangxue Granules (Approval No. Z20120009; Tianchang Yifan Pharmaceutical Co., Ltd.), 3 times/d. The ingredients include Astragalus, Codonopsis, Ligustrum lucidum, Polygonum multiflorum, Angelica sinensis, Rehmannia glutinosa, Chixueteng, Atractylodes, wolfberry, Poria, Chinese yam, Ejiao, Cornus officinalis, Polygonatum chinensis, Rhizoma Drynariae, Chicken Neijin, Malt, and dried tangerine peel. Excipients are dextrin, steviol glycosides.

Outcome measures

(1) Treatment efficiency. Markedly effective: The B-ultrasound showed that the patients' fibroids were reduced by more than 50% and there was no uterine bleeding. Effective: The patients' fibroids were reduced by between 25% and 50%, and the patients' clinical symptoms and uterine bleeding were significantly mitigated. Ineffective: No improvement or aggravation of clinical symptoms and uterine bleeding in the patients was observed.

(2) Incidence of adverse reactions. Adverse reactions including fibroid volume, uterine volume and clinical indexes were recorded and compared between the two groups.

(3) Hematocrit (HCT) and hemoglobin (Hb) levels. 2mL of cubital venous blood was collected from patients before surgery and 1 day after surgery and placed in sterile test tubes. The HCT and Hb levels of patients were detected by an automatic blood analyzer (Japan Sysmex, SYSMEXXE-2100).

(4) Uterine and fibroids volume. B-ultrasonography was performed before and after treatment to record the size of uterus and fibroids in the two groups.

STATISTICAL ANALYSES

The data in the present study were analyzed using SPSS 20.0 software and GraphPad Prism 7 (GraphPad Software, San Diego, USA) was adopted for image visualization. The study included both count and measurement data, which were analyzed via the chi-square test, t-test and normality test. P<0.05 suggests a significant difference.

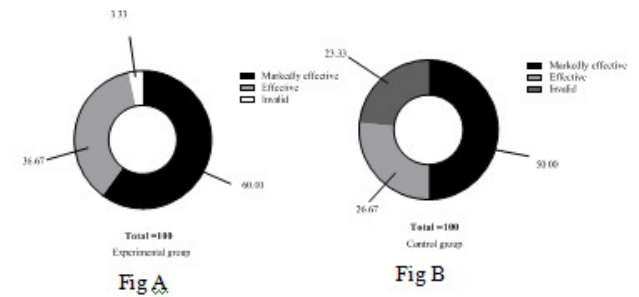
RESULTS

Baseline patient characteristics

The two groups showed comparable baseline characteristics (P>0.05, table 1).

Treatment efficiency

The experimental group showed significantly higher total treatment efficiency than the control group (P<0.05, fig. 1).

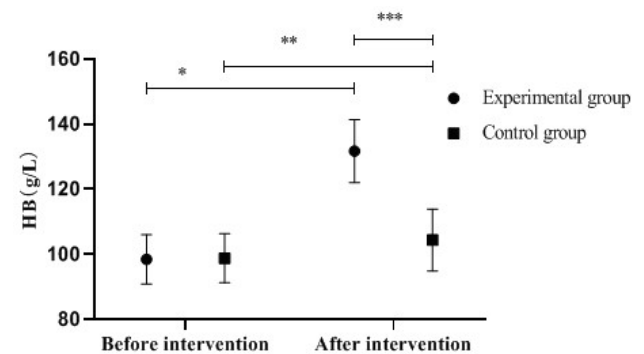


Note: Fig. A represents the treatment efficiency of the experimental group; Figure B represents the treatment efficiency of the control group.

In the experimental group, the markedly effective rate was 60.00% (18/30), the effective rate was 36.67% (11/30), The ineffective rate was 3.33% (1/30), with a total effective rate of 96.67% (29/30).

In the control group, the markedly effective rate was 50.00% (15/30), the effective rate was 26.67% (8/30), the ineffective rate was 23.33% (7/30), with a total effective rate of 76.67% (23/30). There was a significant difference between the two groups after treatment (x²=5.192, P<0.05).

Fig. 1: Comparison of treatment efficiency between the two groups [n(%)]



Note: The abscissa indicates before and after treatment, and the coordinate indicates the HB levels, g/L.

The HB levels of patients in the experimental group before and after treatment were (98.46±7.54) g/L and (131.72±9.67) g/L, respectively.

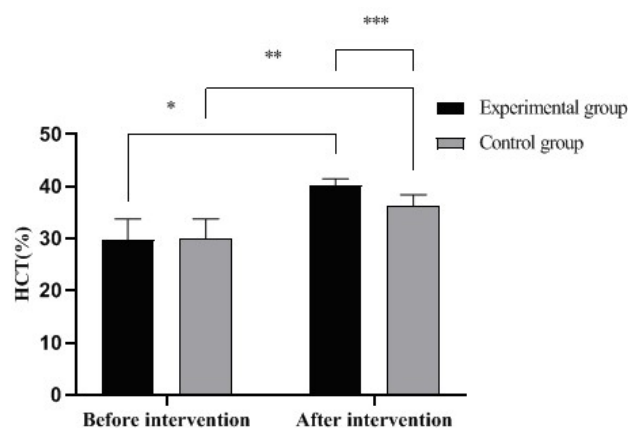
The HB levels of patients in the control group before and after treatment were (98.74±7.53) g/L and (104.38±9.54) g/L, respectively.

*indicates a significant difference in the HB levels of patients in the experimental group before and after treatment (t=14.856, P<0.05).

**indicates a significant difference in the HB levels of patients in the control group before and after treatment (t=2.542, P<0.05).

***indicates a significant difference in the HB levels between the two groups of patients after treatment ($t=11.024$, $P<0.05$).

Fig. 2: Comparison of HB levels between the two groups ($\bar{x} \pm s$).



Note: The abscissa indicates before and after the treatment, and the ordinate indicates the HCT level, %.

The HCT levels of patients in the experimental group before and after treatment were (29.83±3.96) %, (40.23±1.24) %, respectively.

The HCT levels of patients in the control group before and after intervention were (29.94±3.88) % and (36.27±2.16) %, respectively.

* indicates a significant difference in the HCT levels of patients in the experimental group before and after treatment ($t=13.727$, $P<0.05$).

** indicates a significant difference in the HCT levels of patients in the control group before and after treatment ($t=7.807$, $P<0.05$).

*** indicates a significant difference in the HCT levels between the two groups of patients after treatment ($t=8.709$, $P<0.05$).

Fig. 3: Comparison of HCT between two groups ($\bar{x} \pm s$)

Incidence of adverse reactions

The experimental group showed a lower incidence of adverse reactions than the control group ($P<0.05$, table 2).

Fibroid volume and uterine volume

Patients in the experimental group showed significantly smaller fibroid volume and uterine volume than the control group ($P<0.05$, table 3).

HB levels

The experimental group showed significantly higher HB levels than the control group ($P<0.05$, fig. 2).

HCT

The experimental group had a significantly higher HCT level than the control group ($P<0.05$, fig. 3).

Hemorheological indexes

Combined therapy of mifepristone plus Shenqi Yangxue Granules resulted in showed lower erythrocyte aggregation index, erythrocyte sedimentation rate, in

patients in the experimental group than those receiving mifepristone in the control group ($P<0.05$, table 4).

DISCUSSION

Hysteromyoma is a common benign tumour in clinical practice and progressively grows in size with time if no effective treatment is available, which poses a serious threat to the health and safety of patients. Fibroids are relatively slow-growing with insidious symptoms and obvious clinical symptoms usually indicate advanced progression of the disease (Dzuba *et al.*, 2020; Frye *et al.*, 2020; Guilbert *et al.*, 2020; Hcini *et al.*, 2020; Rodriguez and Gulmezoglu, 2020). The incidence of hysteromyoma in China has presented a year-on-year increase over the past few years. The main clinical symptoms of patients include prolonged periods, shortened menstrual cycles, and excessive bleeding, which are associated with miscarriage and infertility. Currently, fibroids are clinically considered sex hormone-dependent and are mainly attributed to excessive progesterone and estrogen in the body. In addition, endocrine function and blood rheology abnormalities contribute significantly to the development of hysteromyoma. Research by EHRNSTÉN LISA *et al* (Ehrnsten *et al.*, 2020) showed that the development of hysteromyoma is not related to high concentrations of estrogen and progesterone in peripheral blood but in the local tissues. The study by CHECK *et al.* (Check *et al.*, 2020) revealed that the cytoplasmic and nuclear contents, as well as the estrogen and progesterone contents, were all significantly higher in the fibroid tissue than in the same myometrium, confirming a close correlation between the development of hysteromyoma and the irritability by progesterone. MUNRO *et al* (Munro *et al.*, 2020) reported that the blood of patients with hysteromyoma is generally in a hypercoagulable state. The higher level of hemorheological indexes indicates the higher viscosity of blood in the body and the relatively poorer microcirculatory function, which seriously undermines the repair of tissues. The difference between hysteromyoma with anemia and ordinary dystrophic anemia is that the former requires diagnosis and treatment of the cause to achieve hemostasis due to the hysteromyoma. At the current stage, surgical and pharmacological treatments are the mainstays of treatment (El-Agwany, 2018; Kim *et al.*, 2021; Osorio *et al.*, 2021; Ota *et al.*, 2020; Wang *et al.*, 2020). However, disease recurrence may occur after discontinuation of the medication. Patients with hysteromyoma with anemia require long-term postoperative recovery, whereby anemia prolongs recovery and impairs the patient's immunity, thereby compromising the patient's quality of life. Shenqi Yangxue Granules contains dried human placenta, tortoise carapace, ox marrow, deer blood, deer antler, deer horn glue and other medicines that nourish the blood and promote blood circulation to alleviate the symptoms of anemia.

Table 1: Comparison of general information between the two groups of patients [n(%)]

	Experimental group (n=30)	Control group (n=30)	χ^2 or t	P
Age (years)	44.23±7.21	48±5.20	2.243	0.033
BMI (kg/m ²)	26.27±1.59	25.89±1.63	0.914	0.365
Comorbidities				
Diabetes	6(20.00)	4(13.33)	0.480	0.488
Hypertension	5(16.67)	3(10.00)	0.577	0.448
Place of residence			0.278	0.598
Urban	19(63.33)	17(56.67)		
Rural	11(36.67)	13(43.33)		
Education level				
University	1(3.33)	1(3.33)	≤0.001	1.000
High School	8(26.67)	9(30.00)	0.082	0.774
Primary School	21(70.00)	20(66.67)	0.077	0.781

Table 2: Comparison of the incidence of adverse reactions between the two groups of patients [n(%)]

Groups	N	Headache	Insomnia	Nausea and vomiting	Total incidence of adverse reactions
Experimental group	30	0(0.00)	0(0.00)	1(3.33)	1(3.33)
Control group	30	2(6.67)	3(10.00)	4(13.33)	9(30.00)
χ^2					7.680
P					<0.05

Table 3: Comparison of fibroid volume and uterine volume in the two groups ($x \pm s$)

Groups	N	Fibroid volume		Uterine volume	
		Before treatment	After treatment	Before treatment	After treatment
Experimental group	30	15.43±4.28	7.12±2.31	129.34±34.17	91.34±15.97
Control group	30	15.57±4.16	10.56±1.14	129.02±34.96	110.24±23.53
t		0.128	7.314	0.036	3.640
P		0.765	0.036	0.723	0.012

Table 4: Comparison of hemorheological indexes between the two groups ($x \pm s$)

Groups	N	Erythrocyte aggregation index	Erythrocyte sedimentation rate
Experimental group	30	2.17±0.84	16.34±1.23
Control group	30	3.12±0.74	19.56±1.19
t		4.648	10.305
P		0.033	0.021

Mifepristone is a new strong anti-progestational drug in clinical practice and is extensively used for gynecological diseases. Relevant studies have reported that mifepristone inhibits endometrial cell separation by lowering progesterone receptor activity (Clements *et al.*, 2020; D'Hoore *et al.*, 2020; Dhanani *et al.*, 2020; Mollier *et al.*, 2020) and promotes endometrial cell apoptosis. As an anti-glucocorticoid and anti-progesterone steroid, mifepristone binds to the progesterone receptor to reduce progesterone activity, effectively inhibits progesterone action, lyses the ovary for the corpus luteum, reduces progesterone and estrogen levels and decreases ovulation in patients. In addition, mifepristone can effectively potentiate the non-competitive anti-estrogenic effect and inhibit the hypothalamic-pituitary-ovarian axis to suppress hormone secretion. It is also effective in

inhibiting the epithelial growth factor in the fibroid tissue, giving rise to a decrease in uterine artery blood flow and energy metabolism of the fibroid tissue, and eventually causing the necrosis of the fibroid secondary to hypoxia, a reduction in the size of the fibroid and amenorrhea in patients (Frijlingh *et al.*, 2020).

Traditional Chinese medicine mainly adopts the methods of nourishing qi and nourishing blood, nourishing the spleen and stomach, etc. to treat this disease. The drug composition of Shenqi Yangxue Granules includes Donkey-hide gelatin, antler gum, tortoiseshell gum, deer blood, rehmannia glutinosa, white peony root, angelica, beef marrow, heche, Codonopsis, Astragalus (honey), Atractylodes (bran fried), velvet antler, Poria, Polygonum multiflorum, jujube, hawthorn (Fried) Malt (Fried),

endothelium corneum gigeriae galli (Fried) Anemarrhena (Salt), Rhubarb (Wine), Peanut Dressing.

Among them, donkey-hide gelatin is flat in nature, can nourish blood and nourish yin; tortoiseshell gum is flat in nature, sweet in taste, can nourish yin and reduce fever, nourish blood and stop bleeding; deer horn glue is warm in nature, can warm the liver and kidney, nourish essence and nourish blood; deer blood can nourish blood, clears blood and removes blood stasis; heche can nourish blood and replenish qi, benefits yang and replenish essence; deer antler can replenish kidney, invigorate essence and nourish blood; Poria can diuretic dampness, invigorating the spleen and calming the heart and soothe the nerves; Astragalus can invigorate Qi and astringe sweat and improve the body's immunity; Angelica can nourish blood, activate blood, regulate the body's immunity; Codonopsis can invigorate Qi and strengthen the spleen; Rehmannia glutinosa can nourish blood and nourish yin, nourish blood and tonify deficiency; Atractylodes Rhizoma can strengthen the spleen and eliminate dampness, nourish qi and nourish blood. The use of Shenqi Yangxue Granules for anemia patients can play a role in strengthening the spleen. The function of kidney, blood production and essence filling can improve their immunity and prevent their disease from recurring. Using mifepristone combined with Shenqi Yangxue Granules to treat anemia and hysteromyoma can promote the operation of qi and blood in patients, improve their immunity and then reduce the recurrence rate of the disease. In addition, it improves the nutritional status of patients, and maintains their red blood cell count, hemoglobin concentration, platelet count and other indicators within the normal range. The current study showed a lower incidence of adverse reactions in the experimental group than that in the control group ($P < 0.05$), which is similar to the findings of SPARIC *et al* (Sparic *et al.*, 2020), which demonstrated that "the incidence of adverse reactions in the observation group was significantly lower than that in the control group (4.2% vs. 17.8%, $P < 0.05$). It indicates that mifepristone plus Shenqi Yangxue Granules for the treatment of patients with hysteromyoma combined with anemia effectively reduces the incidence of adverse effects in patients with a high safety profile.

CONCLUSION

Mifepristone plus Shenqi Yangxue Granules for patients with hysteromyoma combined with anemia mitigates the symptoms of patients and reduces the incidence of adverse reactions, with a high safety profile.

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