

Original Article

Chinese medicinal plants for advanced endometriosis after conservative surgery: a prospective, multi-center and controlled trial

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Abstract: The trial was to explore the effects of Chinese medicinal plants (CMP) treatment on the advanced endometriosis (stage III-IV) after conservative surgery. A prospective, multi-center and controlled trial was conducted from June 2012 to September 2013. Sixty-five post-operative women with advanced endometriosis (stage III-IV) after conservative surgery were included in the trial. They had undergone laparoscopic surgical excision of the endometriosis lesions and the diagnosis of endometriosis was confirmed by pathological examination. The patients received either CMP treatment or goserelin acetate sustained-release depot treatment (as comparison) according to the willingness of the patients. In the post-treatment follow-up visit at 6 and 12 months, the patients were respectively undergone ultrasonic and gynecological examinations. The serum levels of cancer antigen 125 (CA-125) and interleukin 18 (IL-18) were also detected in the post-treatment follow-up visit at 12 months. We found that in the post-treatment follow-up visit at 6 months, the recurrence rate of CMP group and comparison group was 1/31 (3.23%) and 1/34 (2.94%), respectively. In the post-treatment follow-up visit at 12 months, the recurrence rate of CMP group and comparison group was 5/31 (16.13%) and 6/34 (17.65%), respectively. There were no significant differences between the two groups ($P>0.05$). The serum levels of CA-125 and IL-18 significantly decreased in both of the two groups ($P<0.05$) and no marked differences existed between them on the serum levels of IL-18 ($P>0.05$). The serum CA-125 levels of CMP group were significantly lower than those of the comparison group ($P<0.05$). No adverse effect was reported in both of the two groups during the research and the follow-up period. It concluded that CMP showed promise in preventing the recurrence of stage III-IV endometriosis after conservative surgery, although the conclusion is somewhat limited due to the small size of the trial.

Keywords: Chinese medicinal plants (CMP), endometriosis, cancer antigen 125 (CA-125), interleukin 18 (IL-18)

Introduction

Endometriosis, firstly described in 1860 [1], is a common gynecological disease, which affects approximately 10% of reproductive-aged women and 20% to 50% of infertile women [2]. It is the third leading cause of gynecologic hospitalization in the United States [3]. Surgery is the conventional medical treatment for endometriosis with the significant short-term relief effects, however, the post-operative recurrence is common, especially for those women with advanced endometriosis (stage III-IV) [4-6].

Chinese medicinal plants (CMP) have eminent advantages in treating endometriosis [7-10].

CMP provides an alternative option that reduces the incidence rate of surgery in endometriosis patients [11]. A holistic approach of CMP and hypnotherapy was found to reduce the pain and increase birth rates of the patients with therapy-refractory endometriosis [8]. Delphi, a method defined as a series of sequential questionnaires or rounds, that seeks to gain the most reliable consensus of opinion from a group of experts [12], was applied to establish good practice guidelines for a feasibility study exploring the role of CMP in the treatment of endometriosis [13]. The Delphi process identified Qi (vital energy) and Blood stasis as the two diagnostic categories most commonly found in

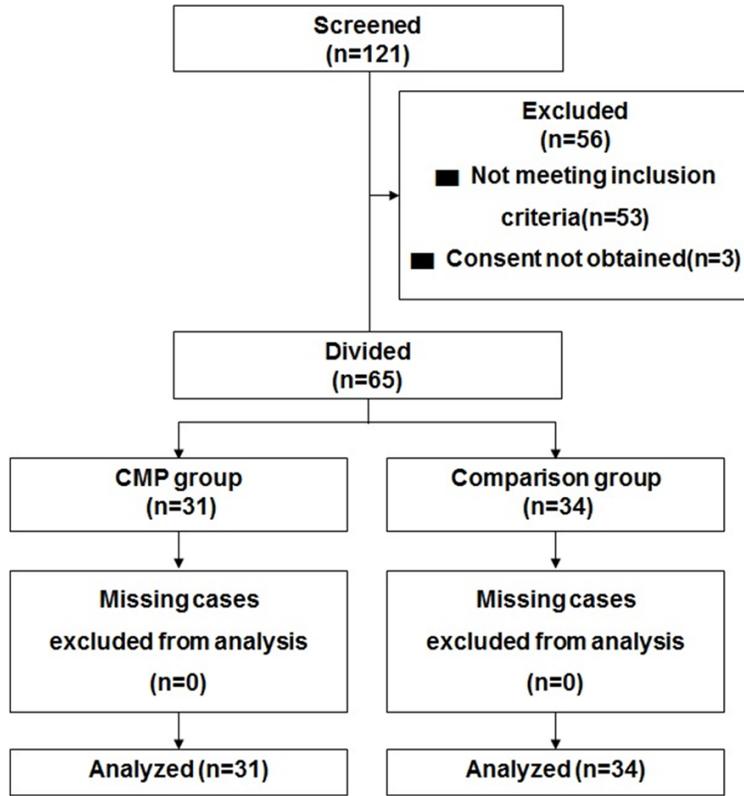


Figure 1. The flow chart of the progress of participants through the trial.

endometriosis, whereas Blood deficiency and Kidney Yang deficiency were also considered relatively common [13], which has provided a scientific basis to further explore the effects of CMP in treating endometriosis. However, few researches have been exclusively conducted on the effects of CMP in the post-operational treatment of endometriosis. Whether CMP has positive effects in preventing the recurrence of advanced endometriosis after conservative surgery? The prospective, multi-center and controlled trial was designed to address it.

Subjects and methods

Subjects

The prospective, multi-center and controlled trial was conducted from June 2012 to September 2013 in Women’s Hospital, School of Medicine, Zhejiang University (Hangzhou, China), the 2nd Hospital, Heilongjiang University of Chinese Medicine (Harbin, China) and the First People’s Hospital of Yuhang District (Hangzhou, China). A total of 65 post-operative

women with stage III-IV endometriosis after conservative surgery were included in the trial. They had undergone laparoscopic surgical excision of the endometriosis lesions 4-6 weeks before they were recruited in the trial and the diagnosis of endometriosis was confirmed by pathological examination. All of the 65 women had no history of hypertension, heart diseases and diabetes mellitus, none of them took any hormones in the past six months before the laparoscopic surgical operation. All the patients did not suffer from any other diseases through gynecologic examinations and laboratory tests.

Group and administration

The post-operative patients with endometriosis of stage III-IV were divided into either CMP group or goserelin acetate sustained-release depot group (comparison group) according to the willingness of the patients. Having been divided, the CMP group had 31 cases and the comparison group 34 cases. Ethical approval and permission to conduct the study were obtained from the Local Ethical Committee. The aim and methodology of the study were explained to the patients. Voluntary participation was requested and informed consent was obtained. Each participant of the two groups received a physical examination, a routine blood examination, a routine uronoscopy, a liver function test and a renal function test respectively one day before the treatment started and one day after the treatment ended. In the statistical analysis, all of the women were included without missing cases during the research and the post-treatment follow-up visits at 6 and 12 months (**Figure 1**).

The formula of CMP is as follows: 30 g of Common Lophatherum, 20 g of Radix Paeoniae Rubra, 20 g of Rhizoma Curcumae and 20 g of Radix Bupleuri. All the herbs were administered

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Table 1. The baseline characteristics

Item	Comparison group (n=34)	CMP group (n=31)
Age (years)	34.79±5.24	32.58±4.92
BMI (kg/m ²)	23.01±4.98	24.44±5.87
Artificial abortion (cases)	14 (41.18%)	13 (41.94%)
Married/cohabitation (cases)	19 (79.41%)	24 (77.42%)
Never married (cases)	4 (11.76%)	3 (9.68%)
Women with children (cases)	17 (50.00%)	18 (58.06%)
Duration of endometriosis before operation (month)	24.90±8.14	26.01±7.15

Notes: Data were shown as mean ± SD; **P*<0.05, compared with the comparison group; CMP: Chinese medicinal plants; BMI: body mass index.

Table 2. The serum levels of CA-125 and IL-18 before and after treatment

Item	Comparison group (n=34)		CMP group (n=31)	
	Pre-treatment	Post-treatment follow-up visit at 12 months	Pre-treatment	Post-treatment follow-up visit at 12 months
CA-125 (U/ml)	94.21±20.11	35.47±7.19 [#]	91.23±18.76	25.12±6.17 ^{*,#}
IL-18 (pg/ml)	103.22±24.55	67.11±9.13 [#]	109.51±23.98	70.01±10.98 [#]

Note: Data were shown as mean ± SD; CA-125: cancer antigen 125; IL-18: interleukin 18; **P*<0.05, compared with the comparison group; #*P*<0.05, compared with pre-treatment in the same group.

within the standard dosage levels. The herbs were provided by the pharmacy departments of individual centers with a national CMP standard. The patients were instructed to orally take one dosage a day for twelve consecutive weeks. A two-week supply was dispensed at each treatment visit. Subjects were asked not to modify their dietary pattern during the research period.

The patients in the comparison group received anterior abdominal subcutaneous injection with goserelin acetate sustained-release depot (made by AstraZeneca China Pharmaceutical Co., Ltd, Wuxi, China), in the dosage of 3.6 mg once every 28 days for 12 consecutive weeks.

Index and method

All the patients completed the 12-weeks treatment. In the post-treatment follow-up visits at 6 and 12 months, the patients were respectively undergone ultrasonic and gynecological examinations. One day before the treatment and in the post-treatment follow-up visit at 12 months, the blood samples were taken and the serum levels of cancer antigen 125 (CA-125) were respectively detected by chemiluminescent

assays (Abbott laboratories, PA, USA). The serum levels of interleukin 18 (IL-18) were measured by enzyme-linked immunosorbent assay (ELISA, provided by Santa Cruz Biotechnology, Santa Cruz, CA, USA).

Data analysis

Results were analyzed by an independent university statistician using Statistical Package for Social Sciences (SPSS 16.0 for Windows), a computer software. Non-parametric Mann-Whitney tests and Analysis of variance (ANOVA) were used to analyze the data. A 5% significance level (*P*<0.05) and two-tailed tests were used for all hypothesis tests.

Results

The baseline characteristics

There were no significant differences between the two groups on all the baseline characteristics (*P*>0.05) (Table 1).

The recurrence rates of endometriosis

In post-treatment follow-up visit at 6 months, the recurrence rate of CMP group and comparison group was 1/31 (3.23%) and 1/34 (2.94%), respectively. In post-treatment follow-up visit at 12 months, the recurrence rate of CMP group and comparison group was 5/31 (16.13%) and 6/34 (17.65%), respectively. There were no significant differences between the two groups (*P*>0.05).

Serum levels of CA-125 and IL-18

As shown in Table 2, there were no significant differences between the two groups on the serum levels of CA-125 and IL-18 before treatment (*P*>0.05). In the post-treatment follow-up visit at 12 months, the serum levels of CA-125 and IL-18 were significantly decreased in both

of the two groups ($P<0.05$) and no marked differences existed between them on the serum levels of IL-18 ($P>0.05$). However, the serum CA-125 levels of CMP group were significantly lower than those of the comparison group ($P<0.05$).

Adverse result

No side-effect was reported in either of the two groups during the research and the follow-up period.

Discussion

As we know, the laparoscopic ovarian cystectomy offered the lowest risk of recurrence and the highest chance of spontaneous pregnancy rate, however, it definitely risked marked injury to the ovarian functions [14, 15]. Although the surgical excision of endometriosis lesions significantly alleviated pain symptoms [16], they may recur after surgery and most of the patients were unwilling to accept a second operation [17]. Medical treatment can be used as a first line therapy to treat recurrent symptoms after surgery or prevent recurrence of the disease [18]. We found in the trial that CMP showed promise in preventing the recurrence of stage III-IV endometriosis after conservative surgery, and no side-effect was reported in either of the two groups during the research and the follow-up period.

As the most consistently studied glycoprotein in endometriosis, CA125 is more accurate in diagnosing advanced endometriosis [19-21], and a correlation existed between the CA-125 levels and the stage of endometriosis [22, 23]. The serum CA-125 levels were significantly increased in the patients with ovarian and mixed endometriosis lesions compared with those who had exclusively extraovarian foci [24]. The correlation between CA-125 and the surgical as well as pathologic finding of ovarian and deep endometriosis was found to be statistically significant [24]. IL-18 is among the cytokines responsible for immune-mediated pathologies [25], which may favor the progression of endometriosis [26]. IL-18-607 A homozygote and A allele were positively correlated with the risk of developing endometriosis or the stage of endometriosis [27]. In this trial, we found that the serum levels of CA-125 and IL-18 significantly decreased in both of the two groups and

no marked differences existed between them on the serum levels of IL-18, however, the serum CA-125 levels of CMP group were significantly lower than those of the comparison group. We found in the trial that CMP showed promise in preventing the recurrence of stage III-IV endometriosis after conservative surgery. However, the conclusion may be somewhat limited due to the limited patients. A large-size, randomized, multi-centre, double-blinded and placebo-controlled trials are supposed to be conducted in the future, and the involved mechanism underlying CMP preventing the recurrence of advanced endometriosis should be addressed.

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Disclosure of conflict of interest

None.

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