Taiwanese Journal of Obstetrics & Gynecology 58 (2019) 218–222

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Effect of danefukang on symptoms and biomarkers in women with endometriosis

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ARTICLE INFO

Article history:
Accepted 14 December 2018

Keywords:
Carbohydrate antigen 125
Danefukang jiangao
Endometriosis
Interleukin-6
Tumor necrosis factor alpha

ABSTRACT

Objective: The purpose of this study was to observe the efficacy of Danefukang (DEFK) soft extract for the treatment of symptoms associated with endometriosis, and its effect on quality of life, the Self-rating Anxiety Scale (SAS) and Self-rating Depression Scale (SDS) scores, and on levels of carbohydrate antigen (CA)-125, tumor necrosis factor (TNF)-α, and interleukin (IL)-6.

Materials and methods: A total of 174 patients with endometriosis treated from January 2010 to December 2013 were randomly divided into a control group treated with mifepristone (n = 87) or DEFK (n = 87). Both groups were treated for 3 months. Symptoms, quality of life, SAS, SD scores, and levels of CA-125, TNF-α, and IL-6 were evaluated before and after treatment.

Results: The effectiveness rate was 93.10% in the DEFK group and 81.61% in the mifepristone control group ($\chi^2 = 4.215$, $P < 0.05$). Treatment with DEFK resulted in a greater improvement in quality of life, SDS, and SAS scores compared with mifepristone (all, $P < 0.05$). DEFK treatment also resulted in a greater decrease of CA-125, TNF-α, and IL-6 levels compared with mifepristone (all, $P < 0.05$).

Conclusion: Based on the current results – improved symptoms, attenuated depression and anxiety, and reduced the levels of pro-inflammatory cytokines and CA-125 -treatment with DEFK is a meaningful option for patients with endometriosis. DEFK fills an unmet need in the pharmacologic treatment of endometriosis.

Introduction

Endometriosis is a common disease estimated to affect 10–15% of reproductive-aged women [1], and is seen in 20–90% of patients with infertility, dysmenorrhea, and chronic pelvic pain [2]. Patients with endometriosis experience periodic dysmenorrhea and persistent pelvic and lumbosacral pain, causing anxiety and depression that significantly impacts quality of life [3–6]. Peritoneal inflammation and an altered immune response has been associated with endometriosis and infertility [1].

Endometriosis is typically diagnosed based on clinical signs and symptoms, and/or identification of pelvic or abdominal endometrial implants by laparoscopy or ultrasound. Women with endometriosis have elevated levels of cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α, and biomarkers such as carbohydrate antigen (CA)-125, which aid in the diagnosis of endometriosis when measured [7,8].

Surgical intervention and pharmacotherapy are common therapies for endometriosis. Since most patients prefer to conserve ovarian function and fertility, radical surgery is not feasible. Thus, conservative pharmacotherapy is an indispensable strategy for the treatment of endometriosis. Western hormonal medical therapies reduce estrogenic stimulation of endometrial implants, causing atrophy to relieve the symptoms of endometriosis [9]. But many patients cannot tolerate the side effects of hormonal therapy and low estrogen levels [9]. Mifepristone is an orally active synthetic steroid with weak anti-androgen and strong anti-progesterone activity in the treatment of endometriosis, however robust studies regarding its effectiveness are lacking [10,11].

Danefukang (DEFK) soft extract (Danefukang Jiangao) is a traditional Chinese drug preparation [12]. Components of DEFK promote blood circulation to dissipate blood stasis and nourish blood for the regulation of menstruation. For example, *Panax*

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https://doi.org/10.1016/j.tjog.2019.01.009

pseudoginseng, a component of DEFK, has been suggested to inhibit inflammation and suppress thrombosis, and exert blood-activating and stasis-dissolving effects [13]. *P. pseudoginseng* also possesses properties of anticoagulation, attenuation of endometriosis, inhibition of adhesions, and regulation of immune function [14]. *Corydalis tuber, another component of DEFK,* is able to replenish blood and regulate menstrual pain. The purpose of this study was to compare the efficacy of mifepristone and DEFK in relieving the symptoms of endometriosis and associated anxiety and depression, as well as their effect on IL-6, TNF-α, and CA-125 levels.

Materials and methods

A total of 1080 patients diagnosed with endometriosis based on gynecological examination and evaluation with B-mode ultrasound were recruited to participate in this study between January 2010 and December 2013. Eligible patients were not pregnant or breast-feeding, had no major organ dysfunction (eg, heart, kidney, or brain), and had no mental illness or cognitive impairment. Patients, who had large lesion and required surgery, were ineligible for the study as were patients who declined to participate in the study. Based on the aforementioned criteria, 906 out of the 1080 patients were excluded, and 174 were included in the study. A flow diagram describing patient selection and distribution is shown in Fig. 1. This study was approved by the Institutional Review Board of Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China, and all patients provided written informed consent for participation in the study.

Patients were randomly divided into two groups. In the control group, mifepristone (Beijing Zizhu Pharmaceutical Co., Ltd.) was administered at the beginning of a menstrual cycle (an initial dose of 12.5 mg, then 6.25 mg once daily for 10 days) for a total of three menstrual cycles. A dose of 15 g DEFK soft extract (Danefukang Jiangao; Dianhong Pharmaceutical Co., Ltd., Kunming, Yunnan, China) was administered to patients in the DEFK group twice daily beginning 15 days before the menstrual cycle for a total of three cycles. The dosing protocol was based on the instructions provided by Dianhong Pharmaceutical Co., Ltd. DEFK contains *Salvia przewalskii*, *Curcuma zedoary*, *Bupleurum marginatum*, *P. pseudoginseng*, *Paeoniae rubra*, *Angelica sinensis*, *Rhizoma sparganii*, *Rhizoma cyperi*, *C. tuber*, and *Glycyrrhiza glabra* (patent number: CN 10473858A).

The severity of endometriosis was classified based on the Revised American Society for Reproductive Medicine classification of endometriosis: 1996 [15]. Therapeutic efficacy was categorized as complete remission, or the disappearance of clinical symptoms and signs, and absence of pelvic masses; partial remission, or the attenuation of clinical symptoms and signs, and reduction in the size of pelvic masses by more than 50% in volume; effective remission, or the attenuation of clinical symptoms and signs, and reduction in the size of pelvic masses by more than 10% in volume; and ineffective remission, or no change or deterioration of clinical symptoms and signs, and increase in the size of focal pelvic masses. The effectiveness rate was calculated as: effectiveness rate = (patients with complete remission + patients with partial remission + patients with effectiveness)/total patients × 100%. Recurrence after discontinuing medication was defined as the return of pelvic pain, dysmenorrhea, and/or dyspareunia, and/or the return of pelvic nodules on clinical examination or imaging.

Before and after therapy, blood (10 ml) was collected from the cubital vein, and serum was harvested and stored at −70 °C until tested. Enzyme-linked immunosorbent assays (ELISA; Abcam, Milton, UK) were used to detect CA-125, TNF-α, and IL-6 levels according to the manufacturer's directions.

Patient quality of life (QOL), anxiety, and depression was evaluated 1–7 days before treatment initiation, and again during the 7 days post treatment. The QOL Scale, Self-rating Anxiety Scale (SAS), and Self-rating Depression Scale (SDS) [6] were also used as part of the patient evaluation. Briefly, the Quality of Life (QOL) Scale consisted of 20 items with a maximum score of 60 points. The final score was calculated as the sum of the scores for each item. Total score was categorized as follows: extremely poor quality of life: <20 points, poor quality of life: 21–30 points, general quality of life: 31–40 points, good quality of life: 41–50 points, very good quality of life: 51–60 points. The Self-Rating Depression Scale (SDS) included questions in 4 dimensions: 1) psychotic affective symptoms (2 items); 2) somatic disorders (8 items); 3) psychomotor disorders (2 items); and 4) depressive disorders (8 items). In China, individuals with an SDS standard score of 50 or greater are

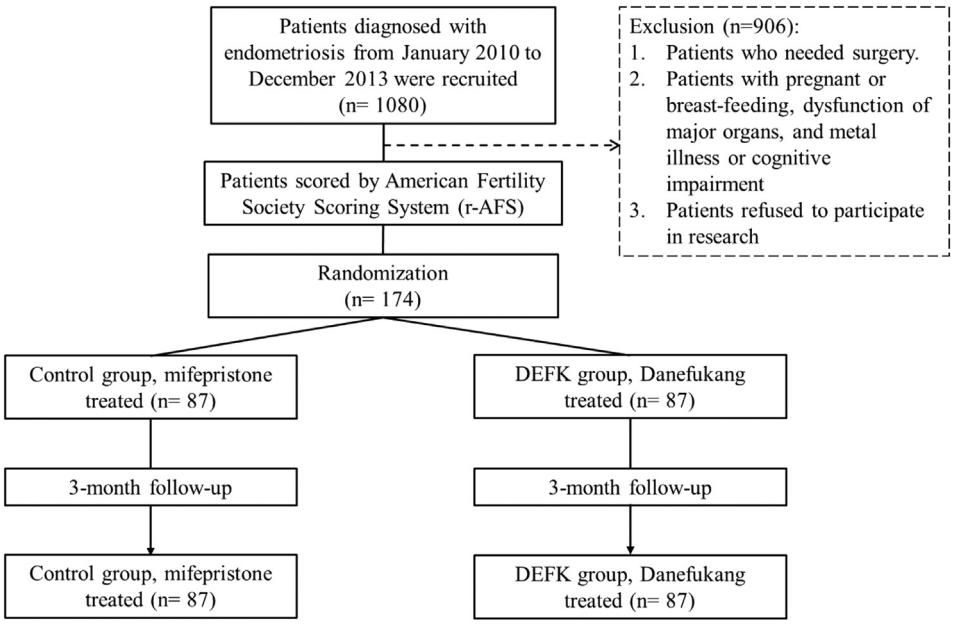

Fig. 1. Flow diagram of patient selection.

classified as having depression. The Self-Rating Anxiety Scale (SAS) is a survey of 20 statements.

Positive-scored items (A, B, C, D) were scored as 1, 2, 3, or 4; the reverse-scored items were scored in the opposite order (eg, 4, 3, 2, 1). The reverse-scored items are 5, 9, 13, 17, and 19. A lower score on the SAS is indicative of reduced anxiety.

Statistical analysis

Quantitative data with a normal distribution were expressed as mean ± standard deviation (SD). An independent sample t test was used for comparisons between the two groups at each time point. Qualitative data were expressed as number and percentage (%), and compared using a chi-square test. A value of $P < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS version 19.0 (IBM, Armonk, NY, USA).

Results

Patients

A total of 174 patients were randomly divided into two groups (n = 87 in the control group; n = 87 in the DEFK group). The mean age of patients in the DEFK group was 30.14 ± 3.98 years, and the mean duration of disease was 3.76 ± 0.78 years (range, 1–12 years). Fifty-six patients were married, and 31 were single. Thirty-eight patients were classified as having mild endometriosis (43.7%), 27 with moderate disease (31.0%), and 22 with severe disease (25.3%) based on the Revised American Society for Reproductive Medicine classification of endometriosis. The mean age of patients in the control group was 30.28 ± 4.32 years (range, 18–47 years), and the mean duration of disease was 3.83 ± 0.84 years (range, 1–12 years). Fifty-four patients were married, and 33 were single. Thirty-five patients were classified as having mild disease (40.2%), 20 with moderate disease (23.0%), 23 with severe disease (26.4%), and 9 patients had missing data. There were no significant differences in age, duration of disease, and disease severity between the two groups (all, $P > 0.05$) (Table 1).

Therapeutic efficacy

As shown in Table 2, the overall effectiveness rate was 93.1% in the DEFK group, which was significantly greater than effectiveness observed in the control group (81.6%) ($\chi^2 = 4.215$, $P < 0.05$).

Quality of life and SDS and SAS scores

QOL, SDS, and SAS scores of the two groups before and after treatment are shown in Table 3. Scores for all three measures were similar between the two groups before treatment (all, $P > 0.05$). After treatment, the DEFK group had a higher QOL score ($P = 0.003$), lower SDS score ($P < 0.001$), and lower SAS score ($P < 0.001$) compared with the control group.

CA-125, TNF-α, and IL-6 levels

Serum CA-125, TNF-α, and IL-6 levels were similar between the two groups before treatment (all, $P > 0.05$; Table 4). After treatment, the levels of all three measures in the DEFK group were significantly lower than those in the control groups (all, $P < 0.001$).

Table 1
Patient demographic and clinical characteristics.

Variable	DEFK, n = 87	Control, n = 87	*p*
Age (y)	30.14 ± 3.98	30.28 ± 4.32	0.824
Disease length of time (y)	3.76 ± 0.78	3.83 ± 0.84	0.57
Married	56 (64.4)	54 (62.1)	0.753
Endometriosis severity[a]			0.705
Mild	38 (43.7)	35 (40.2)	
Moderate	27 (31.0)	20 (23.0)	
Severe	22 (25.3)	23 (26.4)	

DEFK, Danefukang.
Data are presented as mean ± standard deviation, or number (percentage).
[a] There were 9 patients with missing data of endometriosis severity in the control group.

Table 2
Therapeutic efficacy.

Variable	DEFK, n = 87	Control, n = 87	*P*
Recurrence	48 (55.2)	42 (48.3)	<0.05
Effective	33 (37.9)	29 (33.3)	<0.05
Ineffective	6 (6.9)	16 (18.4)	<0.05
Effectiveness rate	54 (93.1)	45 (81.6)	<0.05

Data are presented as number (percent).
DEFK, Danefukang.

Table 3
Quality of life and SDS and SAS scores before and after treatment.

Variable	DEFK, n = 87	Control, n = 87	t[a]	*p*
Quality of life				
Before	39.8 ± 9.6	40.2 ± 10.3	0.258	0.797
After	29.4 ± 7.4	26.1 ± 6.9	3.037	0.003
SDS score				
Before	47.3 ± 4.7	48.1 ± 5.3	1.042	0.299
After	32.8 ± 4.3	38.6 ± 4.9	8.46	<0.001
SAS score				
Before	51.5 ± 5.0	52.3 ± 4.5	1.123	0.263
After	37.0 ± 3.2	41.9 ± 4.1	8.783	<0.001

Data are presented as mean ± standard deviation before treatment and after treatment.
DEFK, Danefukang; SAS, Self-rating Anxiety Scale (SAS); SDS, Self-rating Depression Scale.
[a] Independent sample t test.

Discussion

The results of the current study indicated that DEFK was more effective than mifepristone in relieving symptoms of endometriosis, and was associated with a greater improvement in QOL, as well as SDS and SAS scores. The improvement of SDS and SAS scores suggests that endometriosis may contribute to the development of anxiety and depression. Mifepristone has been used widely used for the treatment of endometriosis, with more than 160 studies

Table 4
Serum CA-125, TNF-α, and IL-6 levels before and after treatment.

Variable	DEFK, n = 87	Control, n = 87	t[a]	*p*
CA-125 (U/ml)				
Before	48.8 ± 7.4	47.3 ± 6.4	1.453	0.148
After	31.72 ± 9.43	38.6 ± 8.3	5.074	<0.001
TNF-α (ng/L)				
Before	32.3 ± 5.5	33.1 ± 4.9	1.076	0.283
After	21.9 ± 5.2	26.6 ± 6.5	5.274	<0.001
IL-6 (ng/L)				
Before	41.9 ± 6.9	42.1 ± 7.4	0.232	0.817
After	26.0 ± 6.0	31.4 ± 6.7	5.598	<0.001

Data are presented as mean ± standard deviation before treatment and after treatment.
CA-125, carbohydrate antigen 125; DEFK, Danefukang; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha.
[a] Independent sample t test.

examining its use published in China alone [10]. A study has shown the effectiveness and safety of mifepristone for the treatment of endometriosis [16]. For these reasons, we believe that comparing the effects of DEFK to mifepristone is a valid method to examine the utility of DEFK for the treatment of endometriosis.

Endometriosis is a chronic condition characterized by endometrial tissue growing outside of the uterus. Common symptoms include chronic pelvic pain, dysmenorrhea, and dyspareunia, all of which can significantly affect QOL [17]. The condition is also associated with infertility, which can also severely affect the QOL of women desiring pregnancy [17].

While the exact pathophysiology of endometriosis has yet to be clarified, it has been demonstrated that immune and inflammatory factors play a significant role [7–9,18,19]. The current study results confirm those of prior studies, which indicate that alleviating symptoms associated with endometriosis decrease levels of inflammatory markers. TNF-α is a biologically active cytokine secreted by monocytes, macrophages, and lymphocytes that supports immune function, and plays an important role in immunopathological damage [20].

The ectopic endometrial tissue in patients with endometriosis may serve as an antigen to stimulate humoral and cellular immunity, which may lead to an increase in the number and activity of macrophages and lymphocytes, and elevated TNF-α expression [21]. There is evidence showing that expression levels of TNF-α is closely related to the severity of endometriosis, and following therapy, those levels are reduced [22]. CA-125 is widely used as a marker of ovarian epithelial tumors, and in distinguishing ovarian cancer from benign lesions and is mainly expressed on the endometrium, peritoneum, and ovarian epithelium. Hyperplasia of the endometrium, peritoneum, or ovarian epithelium may cause CA-125 to be detected in the circulation. It has been demonstrated that CA-125 levels are positively associated with the severity of endometriosis, and it may gradually decrease after pharmacotherapy and/or surgery [23].

IL-6 is a cytokine that stimulates the secretion of other cytokines, regulates immune function, increases the aggregation of leucocytes, and promotes vascular permeability. Elevated levels of CA-125 in patients with endometriosis may persistently stimulate the immune system, leading to an abnormal T cell/B cell ratio resulting in an increase in IL-6 levels [19]. IL-6 may cause immunopathological injury, which may result in the development of endometriosis [18].

Current therapies for endometriosis are primarily aimed at altering estrogen and/or progesterone levels, or inhibiting their effects, and include oral contraceptives, progestin/androgen derivatives, and gonadotropin-releasing hormone (GnRH) agonists [24]. Other therapies have been investigated, including GnRH antagonists, estrogen receptor beta agonists, progesterone receptor modulators, and angiogenesis and aromatase inhibitors [24]. Many of the aforementioned treatments are accompanied by significant side effects as a result of decreased hormone levels and/or androgenic effects.

A substantial amount of research has been devoted to finding complementary and alternative therapies for the management of endometriosis. A comprehensive review by Kong et al. [9] reported that therapeutic approaches, including herbal products, acupuncture and moxibustion, enema with Chinese herbal medications, and microwave physiotherapy, have shown some degree of effectiveness in relieving symptoms and/or shrinking lesions. The report also summarized the results of more than 10 Chinese herbal preparations and decoctions that have shown comparable or better results than Western medications including danazol, medroxyprogesterone, and mifepristone in human and animal studies [9]. Taken together, the previous studies indicated that herbal preparations were able to alleviate dysmenorrhea and reduce levels of inflammatory markers, including IL-2, -6, and -8, TNF-α, and vascular endothelial growth factor (VEGF), as well as alter levels of other markers that may be associated with endometriosis. The current results demonstrate that DEFK can alleviate symptoms and signs of endometriosis and reduce the levels of inflammatory markers is consistent with these prior studies and adds further evidence that alternative therapies are an effective option for this disease.

It should be noted that the recurrence rate was relatively high in both treatment groups in the current study. This may be due to the relatively short 3-month treatment duration. Mifepristone, like many treatments for endometriosis, is typically administered for 6–12 months, but DEFK is generally only given for 3 months, which is why we chose a treatment duration of 3 months. A longer treatment duration may have reduced the recurrence rate, or resulted in different findings.

There are some limitations of this study that should be considered. While statistical significance was achieved, the number of patients was relatively small. No placebo-controlled group was included in the study, and a blinded or double-blind design was not used, which may have provided more reliable data. Patients were diagnosed with endometriosis based on gynecological examination and B-mode ultrasound findings, and not laparoscopy which is the gold standard for diagnosis of endometriosis. A previous study has shown that a mifepristone dose of 12.5 mg/day showed marked effectiveness in women with endometriosis [25]. Thus, the dose used in this study was relatively small. Like almost all Chinese herbal medicines, the DEFK soft extract is a mixture of multiple ingredients and it remains unclear whether one specific ingredient, or the combination of all ingredients is responsible for the effect. A recent report has demonstrated that DEFK contains Danshen (*Salvia miltiorrhiza*) and Ezhu (*Curcuma zedoaria*), and *S. miltiorrhiza* well-known for its use in treating heart and vascular diseases [26]. Furthermore, the mechanism of action was not studied, nor was specific adverse effects. Lastly, using more objective measures to evaluate outcomes such as the Numeric Pain Rating Scale or ultrasound to evaluate endometriosis would have provided additional information; unfortunately, these were not part of the initial study design. This study was intended as a pilot study to determine if DEFK had any effect in the treatment of endometriosis. The positive results provide the information needed to design a future study with more objective outcome measures.

In summary, DEFK can improve symptoms, attenuate depression and anxiety, and reduce the levels of pro-inflammatory cytokines and CA-125 in patients with endometriosis. Further study of the long-term effectiveness is warranted.

Conflict of interest

All authors declare no conflicts of interest.

Funding

Shanghai Education Commission Key Disciplines Foundation.

Key Discipline and Specialty Foundation of Shanghai Municipal Commission of Health and Family Planning.

Key Discipline Project of Renji Hospital, School of Medicine, Shanghai Jiao Tong University.

Acknowledgment

None.

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