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Case Report

Inhibitory effect of traditional Korean medicine on the recurrent endometriosis after laparoscopic excision: a case report

Hae-Won Kim, Jeong-Eun Yoo*

Dept. of Korean Medicine Obstetrics & Gynecology, College of Korean Medicine, Dae-jeon University, Korea

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ABSTRACT

Endometriosis is a common benign gynecologic tumor, and it can destroy a patient's life. Surgery and hormone therapy are established therapies for endometriosis. However, there are many cases of recurrent endometriosis after conventional therapies. This report presents a case of a patient who has repetitive recurrence of endometriosis after laparoscopic excision and hormone therapy. A 32-years-old female patient first had laparoscopic surgery to remove endometriosis in 2011. The disease recurred two more times after the first excision. Hormone therapy by dienogest and two more laparoscopic surgeries were done in 2012 and 2014. With acupuncture, moxibustion, fumigation therapy, and herbal medicine therapy, endometriosis didn't recur during treatment and observation period of 34 months. Menstrual pain numeric rating scales (NRS) decreased from 2 to none. Shortened menstrual cycle (24 days) after second surgery became longer (26.63 ± 2.28 days) after traditional Korean medicine therapy. This case presents the therapeutic potential of TKM for inhibitory effect on the recurrent endometriosis after laparoscopic excision and hormone therapy.

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1. Introduction

Endometriosis is a condition, in which endometrial cells grow outside of the uterus.¹ It is a common gynecological disease to such a degree that its prevalence ranges from 2% to 22% in asymptomatic women and from 40% to 60% in women with dysmenorrhea.² Endometriosis patients are faced with

an illness which destroys physical, mental and social well-being and up to 50% of patients experience infertility.^{3,4} The definitive diagnosis of endometriosis is based on laparoscopy. Laparoscopic excision is also important for the treatment of endometriosis.⁵

However, about 40% to 75% of patients experience recurrence within 5 to 6 years after the first operation.⁶ J.A. Abbott's

* Corresponding author at: Dept. of Korean Medicine Obstetrics & Gynecology, Dunsan Korean Medicine Hospital of Dae-jeon University, 75 Daeduk-daero 176 beon-gil, Seo-gu, Daejeon 35235, Republic of Korea.

E-mail address: jeyoo@dju.ac.kr (J.-E. Yoo).

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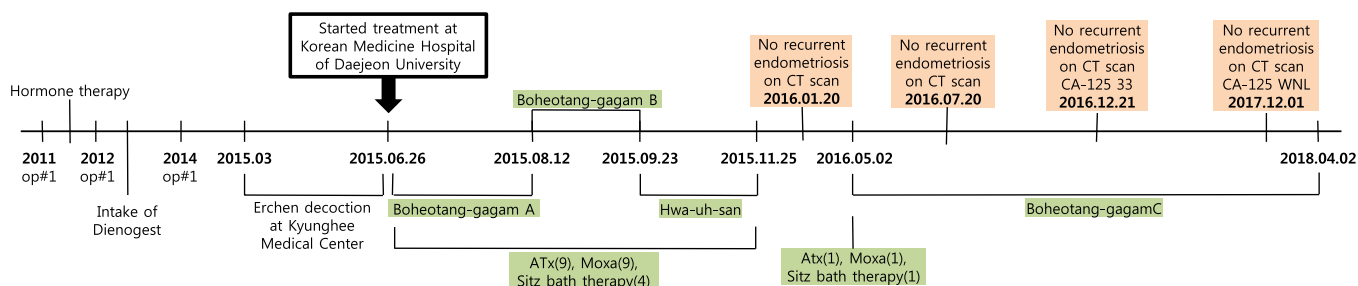


Fig. 1 – The timeline of endometriosis treatment. : therapeutic interventions. : diagnostic examinations. Date is in the order of year, month, and day (YYYY.MM.DD).

study reports that 36% of the patients who had underwent laparoscopic surgery for endometriosis received additional surgery within 5 years of the initial operation. 68% of them had histological recurrence or remaining endometriosis.⁷

According to the American Society for Reproductive Medicine, endometriosis is a chronic disease that requires long-term care to prevent recurrence.⁸ Conventionally, medication is commonly used to inhibit recurrence of post-operative endometriosis, but due to hypoestrogenism-related side effects long-term use of most medications is limited.⁶

This study suggests the successful prevention of recurrence without adverse effect through treatment with traditional Korean medicine (TKM) only in a patient who underwent several laparoscopic surgeries and hormone therapy for endometriosis. This case report could suggest the possibility of prevention of recurrent post-surgical endometriosis through TKM treatment.

2. Case report

2.1. Patient characteristics and medical history

A single, 32-year-old woman attended an Oriental hospital with recurrent endometriosis after conventional treatment. Before the study, agreement on personal information was signed by patient, and the study was approved by the Institutional Review Board at Dunsan Korean medicine hospital of Daejeon University (Deliberation Number: DJDSKH-18-E-04). She received the first laparoscopic surgery in 2011. Endometriosis recurred in 2012 and 2014, and the patient went through two more laparoscopic surgeries and completed intake of Dienogest (DNG, product name Visanne), an oral progestin. She chose the TKM treatment to prevent recurrence and to manage the symptoms after the 3rd surgery.

She was pattern-diagnosed with Phlegm-Dampness at the department of TKM gynecology at Kyunghee Medical Center and had taken Erchen decoction for three months before coming to the Korean Medicine Hospital of Daejeon University on the 26th of June, 2015.

The patient complained of fear of repetitive recurrence, shortening of menstrual cycle (from 28 to 24 days after the second operation), mild lower abdominal and lower back pain during menstruation, clotting menstrual blood, and discharge of leucorrhoea. The pulse diagnosis revealed a string-like pulse

and there was no fur on the tongue during the tongue diagnosis.

The patient had a history of removing a liposarcoma in the bladder, and had fibroadenoma. A uterine myoma sized 1 cm, an ovarian cyst and small uterine polyps were discovered in 2016 and were being observed as well.

2.2. Diagnosis and outcome evaluation

A definitive diagnosis of recurrent endometriosis requires laparoscopy. However, because of ethical and practical problems, it is estimated through recurrence of pain or lesion site on ultrasound, MRI or CT.⁶ The serum CA-125 measurement is a useful marker for predicting recurrence of endometriosis.⁹ In this case, during the TKM treatment, the recurrence was checked through CT scan, recurrence of pain, and serum CA-125 measurement.

The improvement of the patient's general condition was evaluated by checking menstrual pain, the menstrual cycle, and the existence of blood clots in the menstrual blood. Menstrual pain was measured with a numeric rating scale (NRS, 0=None, 10=Unbearable pain). The TKM pattern-diagnosis was performed based on the shape of body type, ordinary symptoms, pulse diagnosis and tongue diagnosis.

2.3. Treatment and progress of symptoms

The patient's pathological state was classified as phlegm-dampness, blood stasis, and qi deficiency in TKM theory. The patient received TKM treatment from the 26th of June, 2015 to the 25th of November, 2015 and from the 2nd of May, 2016 to the 2nd of April, 2018, a total of 29 months at the department of TKM gynecology at Dunsan Korean medicine hospital of Daejeon University. For the initial 10 months, the patient received herbal medicine prescription, acupuncture, moxibustion, and fumigation therapy. The fumigation therapy is a method of exposing the genital area with herbs-infused steam. For the latter 19 months, she received only herbal medicine therapy (Fig. 1).

Herbal medicine was prescribed 27 times during the treatment period. The herbal medicines prescribed for her are Boheotang-gagam and Hwa-uh-san with additional powder form medicine according to symptoms. For the first three months, three rounds of Boheotang-gagam A were prescribed and two rounds of Boheotang-gagam B in concoction form were prescribed to deliver concentrated treatment. After the

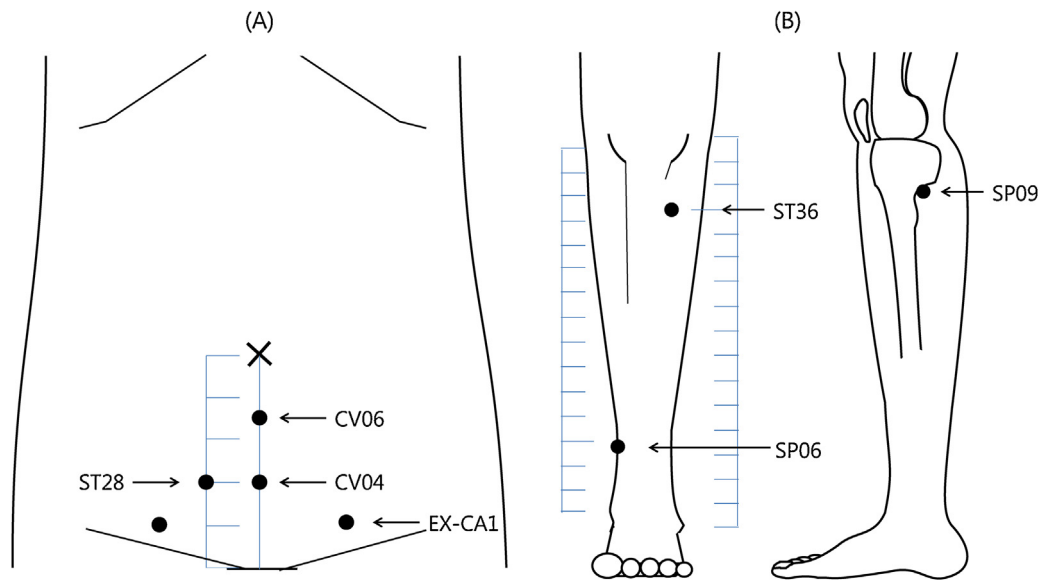


Fig. 2 – Acupoints. (A) CV06, CV04, EX-CA1 (3-chon lateral to CV03). (B) ST36, SP06.

Table 1 – Composition of Drugs

Drug	Composition
Boheotang-gagam A (2015.06.26–2015.07.29)	Atractylodis Rhizoma Alba (6), Angelicae Gigantidis Radix (6) Cnidii Rhizoma (6), Astragali Radix (6), Citri Pericarpium (4) Glycyrrhizae Radix (4), Hoelen (4), Eucommiae Cortex (4) Achyranthis Radix (4), Chaenomelis Fructus (4), Peersicae Semem (4), Carthami Flos (4), Typhae Pollen (6), Lycopi Herba (6), Corydalis Tuber (4), Zingiberis Rhizoma (2), Lonicerae Flos (6), Massa Medicata Fermentata (4), Forsythiae Fructus (4), Cinnamomi Ramulus (2), Spatholobi Caulis (6), Scutellariae Radix (1), Smilacis Rhizoma (6), Amomi Fructus (4), Liripopsis Tuber (4), Cyperi Rhizoma (8), Paeoniae Radix Alba (6), Salviae Miltiorrhizae Radix (6), Moutan Radicis Cortex (4), Oldenlandiae Diffusae Herba (8)
Boheotang-gagam B (2015.08.12–2015.09.05)	Boheotang-gagam A + Pinelliae Rhizoma (4)
Boheotang-gagam C (2016.05.02–2018.02.06)	Atractylodis Rhizoma Alba in Boheotang-gagam B (6)→(8) Citri Pericarpium (4)→(6), Ulmi Macrocarpae Cortex (6)
Hwa-uh-san (2015.09.23–2015.11.25)	Paeoniae Radix Alba, Atractylodis Rhizoma Alba, Alismatis Rhizoma, Angelicae Gigantidis Radix, Hoelen, Atractylodis Rhizoma Alba, Peersicae Semem, Moutan Radicis Cortex, Hoelen, Raeoniae Radix Rubra

concentrated treatment period, Hwa-uh-san was prescribed for five rounds to manage the condition. About 5 month after Hwa-uh-san was finished, 17 rounds of Boheotang-gagam C were administered in pellet form (Table 1).

The acupoints used for acupuncture were CV04, CV06, ST28, EX-CA1, SP06, ST36, SP09 and GV20 (Fig. 2). Acupuncture was administered for a total of ten sessions during the treatment period, each session lasting twenty minutes. Moxibustion was administered 10 times for 20 min on the lower abdomen using the red clay moxibustion method. The fumigation therapy was done a total of five times using Cnidii Fructus for 20 min during each session.

The patient complained of blood clots in menstrual blood and NRS 2 for lower abdominal and lower back pain during the period. Three sessions of acupuncture and moxibustion treatments along with three rounds of Boheotang-gagam A resulted in decrease of blood clots. A following session of acupuncture and moxibustion treatment with a round of Boheotang-gagam B resulted in disappearance of blood clots and menstrual pains. The last time the patient complained about menstrual pains was on the 23rd of November, 2016 to a degree of NRS 1–2, and she has not complained about menstrual pains since then. Blood clots in menstrual blood were observed on the 27th of October, 2015 once and not only the amount decreased on the next menstruation which was on the 22nd of November, 2015, but also all the clots disappeared afterwards.

Menstruation occurred each month based on the last menstrual period (LMP) but the cycle was irregular. She also complained about the shortened menstrual cycle after the 2nd excision. Excluding the period when treatment recessed, the menstrual cycle was on an average of 26.63 ± 2.28 days.

2.4. Diagnosis of recurrence during TKM treatment

During the 29 months of sole TKM treatment period, a CT scan was done four times, on the 20th of January, 2016, the 20th of July, 2016, the 21st of December, 2016, and the 1st of December, 2017. All scans did not show a recurrence of endometriosis. (Fig.3) The serum CA-125 level on the

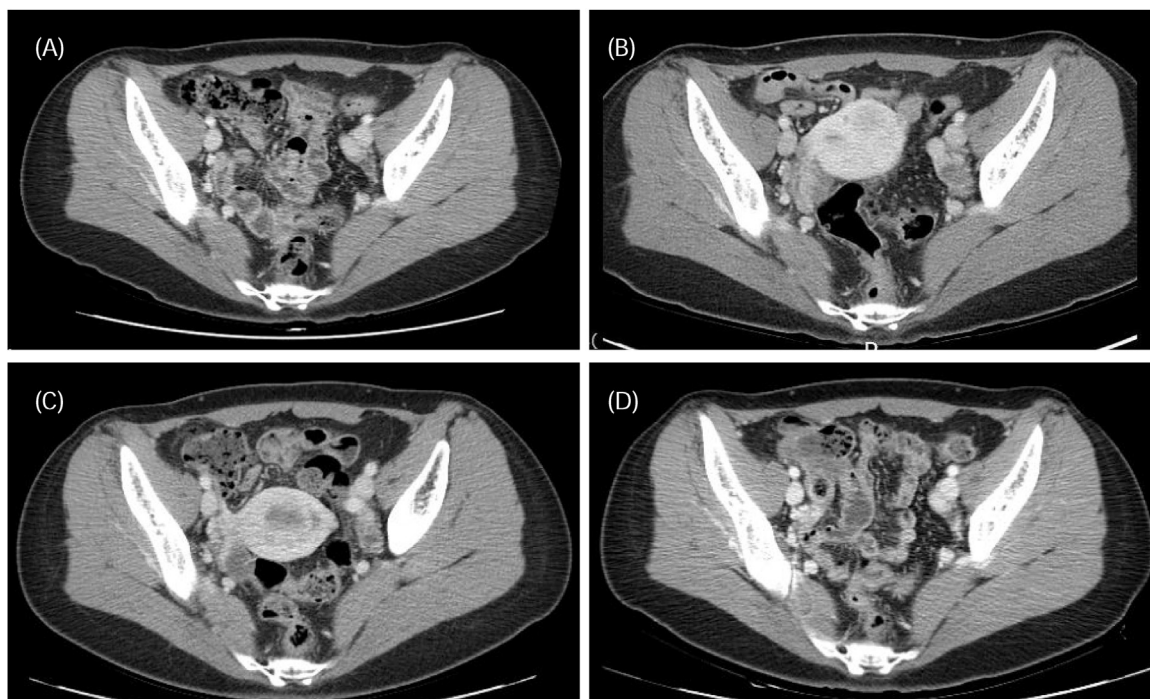


Fig. 3 – CT scan of pelvic area presenting no recurrence of endometriosis. (A) Ten months after starting TKM treatment. (B) Twelve months after starting TKM treatment. (C) Eighteen months after starting TKM treatment. (D) Twenty-nine months after starting TKM treatment.

21st of December, 2016 was 33 which was within normal range.

3. Discussion

Endometriosis is a chronic disease, so it is important to evaluate the long-term applicability and safety as well as the therapeutic effect. However, established hormone therapy poses the problem of side effects during long-term use.¹⁰ The DNG taken by the patient was certified of its effect and safety through long-term trials performed in Europe and Japan, and approved as monotherapy for the treatment of endometriosis in Europe, Japan, Australia, and Singapore.¹¹ Three studies compare GnRHa, the established medicine for Endometriosis. While DNG and GnRHa show similar outcomes, DNG shows less adverse effects in hot flash and bone mineral density contrary to GnRHa.¹²⁻¹⁴

Despite the patient undergoing surgeries and taking DNG, the lesion recurred, so she chose TKM. TKM treatment is different from the conventional therapy, which induces pseudo menopausal state. TKM treatment maintains the ovulation cycle while controlling the condition that aggravates the regurgitation of menstrual blood, therefore has little adverse effects. This is especially helpful in cases where the patient wants to get pregnant.

In TKM theory, endometriosis is seen as a disease related with menstrual pain, lower abdominal pain, metrorrhagia, irregular menstruation, and infertility. It is explained as a pathological state caused by blood stasis. Currently the regurgitation of menstrual blood is supported as the clearest cause

of endometriosis. Since the removal of the regurgitated and transplanted endometrial tissue is related to the immunological surveillance, the deficiency of beneficial qi is a pathological factor.¹⁵

The original version of Boheotang is a prescription that consists of eight herbs; *Atractylodis Rhizoma Alba*, *Ginseng Radix*, *Angelicae Gigantis Radix*, *Cnidii Rhizoma*, *Astragali Radix*, *Citri Pericarpium*, *Glycyrrhizae Radix*, and *Zingiberis Rhizoma*. Boheotang is traditionally used for various symptoms caused by the qi and blood deficiency after childbirth.¹⁶

In Boheotang-gagam A, 21 herbs that make the blood flow smooth and supplement the Liver, Kidney, and digestive organs as well as herbs that eliminate edema were added to the Boheotang to control pain, manage symptoms and prevent recurrence.¹⁷ *Ginseng Radix* which contains approximately 5.22% of ginsenoside is removed from Boheotang. Ginsenoside is a mixture of saponins and is rich in Ginsenosides Rb1, Rc, and Rg1.¹⁸ Rg1 has estrogen-like activity and should be classified as a potent phytoestrogen.¹⁹ Endometriosis is a condition that shows clinical symptoms under the influence of estrogen so *Ginseng Radix* was removed from the prescription.

In Baek's study, Boheotang-gagam was used for post-hysterectomy patients in controlling abdominal pain, lower back pain, and edema as well as for the purpose of recovery from surgery considering that the physical state after hysterectomy was immensely qi and blood deficient and blood clotted which is similar to the state of body after labor.²⁰ Boheotang-gagam A was prescribed to this patient because of repeated recurrence of endometriosis, also the three surgeries had left her deficient in qi and with blood stasis. The

patient had nausea and white thick fur on the tongue after taking Boheotang-gagam A, which are symptoms of damp phlegm. In Boheotang-gagam B, Pinelliae Rhizoma is added to Boheotang-gagam A to remove damp phlegm.

Hwa-uh-san is a powder form medicine mixture of Danggwijakyaksan and Gyejiboknyeonghwan in a 1:1 ratio, which is used to remove blood stasis. Herbal medicine in powder or pellet form is convenient for intake but is known to be less effective than the concoction form. Hwa-uh-san was prescribed to manage symptoms and prevent recurrence after concentrated treatment period. Originally, Hwa-uh-san was prescribed for a month to complete the three-month step of final symptom management on the 25th of November, 2015. However, the patient complained about anxiety from fear of recurrence and wanted continuous management through long-term intake of herbal medicine and so Boheotang-gagam C was manufactured in pellet form to take for 21 months.

Increasing *Atractylodis Rhizoma Alba* and *Citri Pericarpium* in Boheotang-gagam C was for the purpose of removing damp phlegm. According to TKM theory, *Ulmi Macrocarpae Cortex*, which was added in Boheotang-gagam C, has anti-edema and detoxification function, so it has been in frequent use for endometriosis.¹⁸ Recent study reported the extract of *Ulmi Macrocarpae Cortex* inhibits the metastasis of tumor by activating the immune system especially the NK cell.²¹ The decrease in the removal of refluxed endometrial cells in endometriosis patients is mainly due to NK cell activity defects, and partially due to tolerance to NK cell toxicity in the endometrium.²²

GV20, CV04, CV06, ST28, EX-CA1, SP06, ST36, and SP09 were used for acupuncture treatment (Fig. 2). These acupoints are used to add qi and blood, control blood, remove edema and to reduce female genital and lower abdominal pain.²³

Moxibustion was administered on the lower abdomen, and is reported to be applied in various gynecological conditions including primary dysmenorrhea, leukorrhea, primary menstrual pain, etc.^{24–26} Moxibustion on the lower abdomen promotes blood circulation around the uterus through its thermal stimulation. It lowers the circulatory prostaglandin, bradykinin, and histamine, while also increasing oxygen supply to the tissues.²⁷ The fumigation therapy was done to alleviate inflammation and control pain. *Cnidii Fructus* used for the fumigation therapy contains torilin which is known to be effective in anti-inflammation and analgesia.²⁸

Despite the advantage of controlling the inducement of regurgitation of menstrual blood while maintaining ovulatory cycle unlike the conventional treatment, there are a few case reports of endometriosis with TKM therapy, such as the study of Lee's Sobokchukeo-Tang, Seunggeum-Dan, Jo's Gwichulpajing-Tang, Jung's Soshiho-Tang, and Kim's Sobokchukeo-Tang, Banchongsan-gami, Gyeboctang-gami and Daebotang-gami.^{29–32}

The clinical studies on the TKM treatment of endometriosis were done in a range of period from 1.5 month to 22 months (herbal medicine was taken irregularly during the 18 months of that period).^{29,31} In this case report herbal medicine, the major intervention, was taken for 29 months. A follow-up case of herbal medicine intake in such a long period has not been reported to date. This was possible by prescribing comparatively cheap and convenient powder and pellet form medicine.

Considering the high recurrence rate of endometriosis, insisting on one treatment theory is not beneficial for the patient. Along with the surgery and hormone therapy, TKM treatment needs to be used in combination. In this case, the satisfactory level of the patient was high because it controlled the symptoms and prevented recurrence of endometriosis. This study will be a basis for future clinical research related to endometriosis and can suggest a method for preventing recurrence after conventional therapy.

This report is on a single case, there is a lack of supportive evidence and it is hard to generalize. In this case there was no lesion of recurrent endometriosis in the follow-up CT scan and no recurrent pain. The measurement of serum CA-125 was within normal range, thus concluded that there was no recurrence. However, this does not mean a histological complete recovery, so continuous observation is needed by monitoring the patient's symptoms and imaging tests.

In summary, this report suggests the possibility of prevention of recurrent post-surgical endometriosis through TKM treatment.

Conflict of interest

The authors declare no conflict of interest.

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