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Effectiveness of Honghua Ruyi Wan combined with antibiotics for relief of pelvic inflammatory disease pain in women.

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Abstract

Honghua Ruyi Wan (HHRYW) is a traditional Tibetan drug. We designed this study to investigate the effectiveness of HHRYW for relief of pelvic inflammatory disease (PID) pain in women. We performed a multicenter, randomized, double-blind, placebo-controlled trial, and observed the effectiveness and toxicity of HHRYW in combination with moxifloxacin in treating PID. Of the 139 women enrolled in this study, 124 were included in the final analysis. They were divided into the HHRYW group (n=65) and the placebo group (n=59). The baseline age, height, weight, and marital status were well matched between the groups (all: P>0.05). The rate of reduction in tenderness score was significantly greater in the HHRYW group than in the placebo group after 30, 60, and 90 days of treatment. The HHRYW group had a significantly lower subjective visual analogue scale score at 30, 60, and 90 days after treatment. The incidence of adverse reactions was 7.04% (5/71) in the HHRYW group and 10.61% (7/59) in the placebo group. No severe adverse reactions were noted in either group. The combination of HHRYW and antibiotics effectively relieve abdominal pain caused by PID with obvious long-term efficacy and acceptable adverse reactions.

Keywords: Pelvic inflammatory disease, Honghua Ruyi Wan (HHRYW), Relieve abdominal pain, Tibetan medicine.

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Introduction

Pelvic inflammatory disease (PID), which is a common gynecologic disorder in women less than 45 years of age [1], refers to a group of diseases including endometritis and salpingitis that are caused by infection of the female upper genital tract [2]. This condition is usually caused by a sexually transmitted infection and increases the risk for tubal infertility, ectopic pregnancy, and chronic pelvic pain, which can impair the quality of the woman's life [3]. Pelvic pain is the principal symptom of PID [4,5], which can be conceptualized as a chronic regional pain syndrome or functional somatic pain syndrome [6]. The most important aspect of the treatment of PID is the relief of pelvic pain [7], which is a difficult problem [8]. Parenteral broad-spectrum antibiotic therapy with activity against polymicrobial flora, particularly gram-negative aerobes and anaerobes, should be implemented [9]. The International Union against Sexually Transmitted Infections (IUSTI) and the U.S. Centers for Disease Control and Prevention (CDC) have issued treatment recommendations for the management of PID [10]. Traditional Chinese medicine has played an important role in pain relief of PID in China [11].

Traditional Tibetan medicine is based on native knowledge and medical practices in Tibet and traditional Han Chinese, Indian, and Arabic medical theories, and has formed a unique medical system in its two thousand-year history. Honghua Ruyi Wan (HHRYW, or "Safflower Wishful Pill," known as "Guge Sangpei" in Tibetan) is a traditional Tibetan prescription. Modified from the classical "25-ingredient Podophyllum Pill,"

it has proven to be highly effective in the treatment of a variety of gynecological diseases. HHRYW has 25 key ingredients; most can only be found on the Qinghai-Tibet Plateau.

Clinically, HHRYW can alleviate chills and pain, and is particularly effective for management of menstruation disorders [12]. Notably, PID predominantly manifests as pain. HHRYW can decrease the pain response in mice and inhibit granuloma in rats. In addition, HHRYW has certain inhibitory effects on acute inflammation caused by xylene, and thus exerts remarkable anti-inflammatory and analgesic effects.

We investigated the clinical pain relief, effectiveness, and safety of HHRYW combined with antibiotics for treatment of PID. We performed a multicenter, randomized, placebo-controlled, double-blind clinical trial in six tertiary hospitals across China, led by the Peking University First Hospital. This study was approved by the Human Ethics Committee of Peking University First Hospital.

Materials and Methods

Clinical data

A total of 139 female patients who met the diagnostic criteria of PID in any of the six participating hospitals between October 2010 and June 2011 were enrolled in this study. The per-protocol (PP) population was the primary population used for efficacy analysis. This population included all women who fulfilled the study inclusion criteria, had no protocol violations affecting efficacy, and who were at least 80% compliant with the dosing schedule. Among them, 124 patients were included in the PP population: 65 in the HHRYW group and 59 in the placebo group. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of the First Hospital of Peking University, Beijing, China (2010), and our study has been conducted in compliance with the ethical principles for medical research involving human subjects, as stated in the World Medical Association Declaration of Helsinki. Written informed consent was obtained from all participants.
The study group and the control group each included 108 cases calculated in accordance with the quantity of samples [13]. The patients were randomly divided into an experimental group and a control group. In each center, the ratio of patients in the experimental group to the control group was 1:1, so the expected number for each center was 36 cases: 18 cases in the study group and 18 cases in the control group.

The stratified randomization method was used. The random numbers were generated using the SAS software (8.0) program (SAS Institute, Inc., Cary, NC, USA). The random cycle was every six patients. The code of experimental drugs was conducted independently by a third-party statistics company (BC-BIOSTAT Co., Ltd., Chaoyang District, Beijing, China). The subjects received the drug numbers from small to large in the order of entry.

After eight months, the sponsor of this drug clinical trial decided to terminate the study, although no center had enrolled the target number of patients. The participating hospitals were Peking University First Hospital (n=28), Tianjin Central Hospital of Obstetrics and Gynecology (n=19), Obstetrics and Gynecology Hospital of the Medical Center of Fudan University (n=13), the Second Affiliated Hospital of Chongqing Medical University (n=32), the Sixth Affiliated Hospital of Sun Yat-sen University (n=31), and the Affiliated Hospital of Qingdao Hospital (n=16).

Inclusion criteria

The subjects enrolled in this study were women aged 18 to 50 years, and their clinical signs and symptoms met the diagnostic criteria proposed in the Chinese Guidelines on the Diagnosis and Treatment of Pelvic Inflammatory Disease (draft) [14]. The diagnosis of PID was based on the presence of all of the following criteria: pelvic discomfort, direct lower abdominal tenderness, adnexal and cervical motion, and tenderness on bimanual vaginal examination. In addition, patients may have had one of the following additional signs: pyrexia (oral temperature > 38.3°C), abnormal cervical or vaginal mucopurulent discharge, presence of abundant numbers of white blood cells under saline microscopy of vaginal fluid, elevated C-reactive protein levels, erythrocyte and sedimentation rate, and cervical infection, including mucopurulent cervical discharge or positive Gram stain for Gram-negative intracellular diplococci from the endocervix. The most specific criteria for diagnosing PID included the following: endometrial biopsy with histopathological evidence of endometritis; transvaginal sonography or magnetic resonance imaging techniques showing thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex; Doppler studies suggesting pelvic infection (e.g., tubal hyperemia); and laparoscopic abnormalities consistent with PID.

Participants were willing to participate in this research and followed all of the requirements. They were required to understand and comply with the dosage and follow-up plan, and voluntarily signed written informed consent.

Exclusion criteria

Subjects were excluded from the study if any of the following conditions applied: use of a relevant drug in the previous week; diagnosis of concomitant vaginitis caused by *Candida* spp. or vulvovaginal candidiasis. Withdrawal from the study during treatment or follow-up; a history of allergies to the components contained in the study drug or control drug, or to drugs with similar chemical structures; endocrine diseases such as diabetes or Cushing's syndrome, neurological/psychiatric disorders, severe heart/liver/kidney damage, and/or a compromised immune system; pregnant or lactating women or women who were planning to become pregnant; staff directly involved in the study; and subjects who were currently or had previously participated in another clinical study within the past 30 days.

Treatment protocol

Enrolled patients received an experimental or placebo treatment according to the protocol of a randomized, placebo-controlled, double-blind, clinical trial, and underwent regular follow-up.

In this study, every patient in both groups received oral moxifloxacin (400 mg, once a day) for total of 14 days for the treatment of pelvic inflammatory disease. The treatment group included patients who had HHRYW in combination with moxifloxacin. The placebo group included patients given placebo in combination with moxifloxacin [9,10]. The placebo was made from starch, dextrin, and edible pigment. The appearance of the placebo was the same as that of HHRYW. A protective film was placed over the surface of each pill to ensure that the patient could not distinguish the treatment by smell. HHRYW or the placebo (five pills, twice per day) was orally administered shortly after a meal for 1 month while taking moxifloxacin.

Follow-up

Follow-up visits were arranged at 3, 30, 60, and 90 days after treatment. The primary efficacy variable was the clinical response of the PP population at 90 days. Clinical signs and symptoms were assessed. Concomitant medications and adverse events were also recorded, and case report forms were completed.

Evaluation of clinical efficacy

The primary efficacy variable was defined as a reduction in the tenderness score (McCormack scale) [11]. The patients' subjective visual analogue scale (VAS) scores were recorded at the same time. The rate of reduction in tenderness score was calculated as: (baseline score - follow up score)/baseline score. For the tenderness score, four quadrants of the abdomen, cervix, uterus, and bilateral adnexa were scored using a scale of 0 to 3. For the patients' subjective VAS score, a self-rated 10-point VAS was used to measure pain.

The secondary efficacy endpoints were the self-rated VAS score and the rate of improvement in symptoms and signs 3, 30, and 60 days after treatment.

Safety evaluations

Safety evaluations included a physical examination (including vital signs) at enrollment and at 3 and 30 days. Clinical laboratory assessments for blood chemistry and hematological parameters were performed on blood samples taken within 48 h of the first dose of the study drug, and repeated at 3 (for hematological parameters) and 30 days (for blood chemistry).

Statistical analysis

Data are presented as mean ± standard deviation (SD) or median with interquartile ranges unless otherwise indicated. All data were managed using EpiData Software (EpiData Association, Odense, Denmark), and statistical analysis was performed using the SAS 8.0 software package (BC-BIOSTAT Co., Ltd, Chaoyang District, Beijing, China). All tests were two-sided and statistical significance was assumed at $P<0.05$. A Student's t-test was used to test for baseline balance, while the difference of the percentages of married women between the two groups was performed using the Chi-squared test. Assessments of the primary efficacy endpoint and secondary efficacy variables were performed using repeated analysis of covariance (ANCOVA). Repeated measurements analyses were performed using ANCOVA-type linear mixed models. Additionally, differences between subjects were accounted for using random effects.

Results

Comparison of baseline variables

A total of 139 patients were enrolled in this study. Of those, 124 completed the study and comprised the PP population. The PP population included 65 participants in the HHRYW group and 59 in the placebo group.

Baseline age, height, weight, and marital status were well matched between the two groups (all, $P>0.05$). The baseline tenderness score was similar in the two groups. This score was 9.58 ± 4.71 in the HHRYW group and 9.12 ± 4.63 in the placebo group ($Z=-0.7014$, $P=0.483$ (Table 1).

Table 1. *Comparison of baseline variables between the HHRYW and placebo groups*

	n	Age	Height	Weight	Married
HHRYW group	65	34.31 ± 7.82	160.25 ± 4.48	57.12 ± 9.25	87.5%
Placebo group	59	34.46 ± 7.16	160.22 ± 5.36	56.89 ± 7.56	95.2%
t		0.10	0.04	0.15	$\chi^2=1.14$
P		0.9166	0.9692	0.8818	0.2854

Comparison of efficacy

There was a significantly greater increase in tenderness score changes in the HHRYW group than in the placebo group (day 90: $Z=-5.427$, $P=0.0001$). The rate of reduction in tenderness scores 30, 60, and 90 days after treatment was significantly different between the two groups. The tenderness scores were considerably decreased after drug therapy (Table 2). This finding indicates that HHRYW can alleviate the symptoms of PID, particularly after long-term treatment.

The self-rated pain score is a commonly used tool for evaluating the efficacy of an analgesic drug. The VAS scores were significantly lower in the HHRYW group compared with the placebo group (day 90: $Z=4.0507$, $P=0.0001$). The VAS score at 30, 60, and 90 days after treatment was significantly lower in the HHRYW group compared with the placebo group (Table 3). This finding indicates that HHRYW can remarkably

alleviate pain symptoms caused by PID, particularly after long-term treatment.

Table 2. *Rate of reduction in tenderness scores (%) after treatment*

	n	Day 3	Day 30*	Day 60*	N (missing)	Day 90*
HHRYW group	65	51.35 ± 25.17	83.44 ± 20.14	90.60 ± 16.90	63(2)	91.54 ± 15.75
Placebo group	59	40.2 ± 19.53	69.91 ± 25.53	66.13 ± 28.49	59 (0)	65.12 ± 35.81
Z		-1.042	-3.275	-5.256		-5.427
P		0.2975	0.0011	0.0001		0.0001

*P<0.05, compared with the placebo group

Table 3. *Changes in the self-rated VAS score*

	n (missing)	Day 3	Day 30	Day 60	Day 90
HHRYW group	64 (1)	3.48 ± 2.17	1.67 ± 1.92	1.02 ± 1.59	1.08 ± 1.68
Placebo group	59	3.90 ± 1.65	2.91 ± 2.03	2.74 ± 2.01	2.43 ± 2.08
Z		1.313	3.6161	5.1056	4.0507
P		0.1892	0.0003	0.0001	0.0001

Table 4. *Incidence of adverse reactions in the two groups*

	n (missing)	Adverse reactions
HHRYW group	71 (1)	5 (7.04 %)
Placebo group	59	7 (10.61%)

Five patients in the HHRYW group experienced adverse events (mild, n=3; moderate, n=1; and severe, n=1), and six patients in the placebo group suffered from adverse events (mild, n=3; moderate, n=2; and severe, n=1) (P=0.9196) (Table 4). The main adverse reactions included nausea, dizziness, numb lips, vulvovaginal candidiasis, and a low white blood cell count. Nausea was a severe adverse reaction experienced by two patients, and improved after drug withdrawal.

Discussion

PID is a group of diseases (e.g., endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis) caused by infection of the female upper genital tract [15]. Pain is the main clinical manifestation in most patients (>90%) [16]. Inflammation does not affect only a single pelvic organ, but can affect many other adjacent organs and tissues [17]. Furthermore, PID is caused by a variety of pathogens [18]. In addition to sexually transmitted infectious pathogens such as *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, some aerobic and anaerobic bacteria are also involved in the pathogenesis of PID. Most PID cases are caused by the upward spread of pathogenic microorganisms from the vagina, and mixed infections are common [19].

Antibiotics remain the first-line treatment for PID [20]. However, sequelae are common after antibiotic treatment for PID, and its effectiveness is often unsatisfactory [21-23]. In China, traditional Chinese medicine is applied for treatment of PID, and its efficacy has been indicated in previous studies. However, these studies were often poorly designed, and most were non-randomized and non-controlled. Therefore, they could not provide clear and convincing evidence. The current study was a multicenter, randomized, double-blind, placebo-controlled trial, which provided much more reliable evidence for the evaluation of therapeutic drug effects.

We examined the effectiveness of HHRYW in combination with an antibiotic agent (moxifloxacin) in reliving PID pain. Moxifloxacin (400 mg, qd, for 14 consecutive days) has been included in the Chinese Guidelines on the Diagnosis and Treatment of Pelvic Inflammatory Disease (draft). Maiden and Monalisa demonstrated that moxifloxacin was effective in PID treatment. As a broad-spectrum monotherapy, moxifloxacin administration reduces the risk of drug interactions and facilitates monitoring of side effects.

The sequelae of PID remain common and can cause chronic pelvic pain. In the current study, our priority was to determine whether HHRYW could improve clinical pain symptoms in PID patients and reduce long-term pain-related sequelae.

Our study showed that the VAS score was significantly lower in the HHRYW group than in the placebo group 30, 60, and 90 days after treatment. In addition, the decrease in tenderness scores over time was significantly greater in the HHRYW group than in the placebo group. The rate of reduction in the tenderness score was significantly greater in the HHRYW group than in the placebo group after 30, 60, and 90 days of treatment (83.44% *vs.* 69.91%, 90.60 *vs.* 66.13%, and 91.54 *vs.* 65.12%). The HHRYW group had a significantly lower subjective visual analogue scale score at 30, 60, and 90 days of treatment (1.67 *vs.* 2.91, 1.02 *vs.* 2.74, and 1.08 *vs.* 2.43). This finding indicates that HHRYW can remarkably alleviate the pain of PID, particularly after long-term treatment. As indicated by these two efficacy endpoints, the combination of HHRYW and antibiotics has satisfactory effectiveness for PID.

Traditional Tibetan medicine's sophisticated theoretical system is based on the theory of "three factors" (the Tibetan names are Long, Chiba, and Peigen), which is supported by "seven substances" (diet, blood, flesh, fat, bone, marrow, and seminal fluid) and "three excrements" (sweat, urine, and stool) of the human body. These three factors govern the movement and change of the seven substances and three excrements. Under normal physiological conditions, the relationships among the three factors, seven substances, and three excrements are in good balance. However, the excessive rise or fall of one or several factors may cause pathological changes, resulting in Long disease, Chiba disease, or Peigen disease. Accordingly, the treatment for these diseases should also be based on the restoration of balance and harmonization among these factors.

In traditional Tibetan medicine, PID was classified as a Long disease.

As shown in modern traditional Chinese medicine studies, traditional Chinese medicine inhibits bacterial growth, alleviates pain, relieves inflammatory exudate and swelling, reduces the secretion of cytokine-dependent endothelial leukocyte adhesion molecule 1 and CD18, and improves microcirculation in PID patients [24]. Preclinical studies have indicated that HHRYW remarkably reduces the amount of body twisting and prolongs the latency period in mouse models of oxytocin-induced dysmenorrhea. HHRYW also inhibits normal uterine contractions of rats, relieves oxytocin-induced uterine contractions, alleviates the pain response to thermal and chemical stimulation, inhibits granuloma, suppresses xylene-induced acute inflammation, and inhibits contraction of uterine smooth muscle in rat models of oxytocin-induced dysmenorrhea. The above studies showed that HHRYW had good analgesic effects and remarkable anti-inflammatory effects. Therefore, these effects may be the reason why HHRYW is effective in relieving PID pain.

In the current study, the incidence of adverse reactions was not significantly different between the HHRYW group and the placebo group. Furthermore, the main adverse reaction was nausea, which is also a major side effect of moxifloxacin. Therefore, HHRYW is a safe therapy for relief from PID pain.

In summary, the combination of HHRYW and antibiotics effectively relieves PID-induced abdominal pain, particularly after long-term treatment, without increasing adverse reactions. HHRYW is an effective and safe drug for PID.

Conflicts of Interest

None of authors declares that they have no conflicts of interest.

Role of the Funding Source

This post-marketing clinical trial was sponsored by Tibet CheeZheng Tibetan Medicine Company, which produced HHRYW. The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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