ORIGINAL RESEARCH

A Phase III Clinical Trial Evaluating the Efficacy of Yinghua Tablet in the Treatment of Sequelae of Pelvic Inflammatory Disease

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ABSTRACT

Objective • To evaluate the efficacy and safety of the Yinghua tablet in treating sequelae of pelvic inflammatory diseases (PID) that manifest as the syndrome of dampness-heat stasis.

Methods • The experimental group enrolled 360 cases, while the control group enrolled 120 cases. The experimental group took Yinghua tablets three times a day, three tablets each time, and the control group took Fuyankang tablets three times a day, three tablets each time. The treatment course was six weeks. Before treatment, at three weeks and six weeks of treatment, the patients were scored for TCM syndrome, clinical symptoms and, signs, and adverse events during treatment were recorded.

Results • The experimental group included 340 cases, and the control group finally included 114 cases. After six weeks of treatment, statistically significant differences were observed between the two groups in the treatment effect, recovery rate, markedly effective rate, and total effective rate ($P < .05$). The two groups had no significant difference in the effective rate of local signs ($P > .05$). However, the two groups had a significant difference in the total effective rate ($P < .05$). Before and after treatment, traditional Chinese medicine (TCM) symptoms score, symptom sign score, and local sign score were statistically significant ($P < .05$). The incidence of adverse events (AEs) after taking Yinghua Tablets was 3.61% (13 times), of which the incidence of adverse events related to study drugs was 0.28% (1 case). The AEs of Fuyankang Tablets were 1.67% (2 times), of which the incidence of adverse events related to study drugs was 1.67% (2 cases). There was no significant difference in the incidence of AEs between the two groups as compared to Fisher ($P = .3767$), indicating that no serious AEs occurred in either group.

Conclusions • Yinghua tablet was effective and safe in treating sequelae of pelvic inflammatory diseases. (*Altern Ther Health Med.* 2023;29(6):170-175).

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INTRODUCTION

Pelvic inflammatory disease (PID) is a common gynecological disease that frequently occurs in women of childbearing age, encompassing endometritis, salpingitis, ovarian cysts, and pelvic peritonitis.[1] The main clinical manifestations of PID are lower abdominal pain, fever, abnormal increase of vaginal secretions, or abnormal uterine bleeding. If patients do not receive standardized, timely, and effective treatment during the early stages of the disease, a series of sequelae may occur, forming the so-called sequelae of pelvic inflammatory disease (SPID).[2,3] Currently, antibiotics are the main treatment for PID in clinical practice, but they also face the problem of unreasonable use of antibiotics and the generation of drug-resistant bacteria.[4]

Traditional Chinese medicine has a long history in China, and many ancient books describe the symptoms and treatment strategies for PID.[5] Previous studies have found that traditional Chinese medicine can improve the clinical efficacy of PID, shorten the course of the disease, and reduce the occurrence of

sequelae.[6,7] Based on numerous clinical and experimental studies, doctors have varying understandings of the syndrome type and treatment methods for sequelae of SPID.[8]

Yinghua Tablet is a traditional Chinese medicine tablet developed by our company and has obtained qualified clinical drug approval. Its main ingredients include Salvia miltiorrhiza, Sophora flavescens, Taraxacum mongolicum, Rhizoma corydalis vinegaris, Cockscomb, Foeniculum vulgare, and Coix seed. It has been shown to activate blood circulation and remove blood stasis, as well as clear heat and remove dampness.[6-8] This study conducted a Phase III clinical trial of Yinghua Tablet to evaluate its clinical efficacy in treating PID.

MATERIALS AND METHODS

Study Design

The study design for Phase III clinical trials of Yinghua Tablet involved a positive-drug parallel controlled, stratified block randomized, double-blind, multi-center clinical trial design. Patients were randomly assigned to receive either Yinghua Tablet or a placebo, and both groups were treated for a period of four weeks. The primary outcome measure was the clinical efficacy rate, which was determined based on the resolution of symptoms and signs associated with PID and the results of laboratory tests. Secondary outcome measures included changes in vaginal discharge, pain scores, and quality of life assessments. Adverse events were also monitored throughout the trial. The study was conducted between September 2018 and August 2019.

Diagnostic Criteria

The diagnostic criteria for chronic PID in Western medicine are based on the Guiding Principles for Clinical Research of New Chinese Medicines (2002 edition). On the other hand, the criteria for TCM syndrome diagnosis, particularly for dampness-heat and blood-stasis syndrome, are based on the Guiding Principles for Clinical Research of New TCM Drugs published in 2002.[9]

Inclusion Criteria and Exclusion Criteria

Inclusion criteria: (1) The symptoms were consistent with the diagnosis of chronic pelvic inflammatory disease in Western medicine or the diagnosis of damp heat and blood stasis in traditional Chinese medicine; (2) the age ranges from 18 to 50 years; (3) all participants signed the Informed Consent Form.

Exclusion criteria: (1) Pregnant, planned pregnancy, or lactating women; (2) individuals with an allergic constitution or allergic to existing Chinese medicine ingredients; (3) patients with serious primary diseases such as cardiovascular and cerebrovascular, liver, kidney, hematopoietic system, diabetes, and mental illness; (4) patients with gynecological tumor, endometriosis, pelvic venous stasis, tuberculous pelvic inflammatory disease, and other related symptoms; (5) menstrual period lasting more than 15 days or irregular vaginal bleeding; (6) received relevant treatment within two weeks; (7) Patients participating in other clinical trials; (8) Severe cervical erosion; (9) Vaginitis caused by trichomoniasis, mold; (10) Suspected or confirmed history of alcohol and drug abuse, or conditions that are not conducive to the study according to the project situation, such as frequent changes in the work environment, unstable living conditions, or other conditions that may result in loss of follow-up.

Treatment Regimen

Patients who met the inclusion criteria were randomly assigned to two groups at a ratio of 3:1. The experimental group was administered Yinghua Tablet (provided by Shaanxi Sanzheng Shengbang Pharmaceutical Co., LTD., Batch number: 080806), which contained salvia miltiorrhiza, sophora, dandelion, rhizoma corydalis vinegaris, cockscomb, Fructus feniculata, and coix seed. Each tablet contained 0.5 g of the ingredients, and the participants took three tablets three times a day. The control group was given Fuyankang Tablet (produced by Jiangmen Dexin Pharmaceutical Co., LTD., lot number: 080101), which contained Red peony root, Poria cocos, Tricolor, Chinaberry seed, Curcuma, Rhizoma corydalis, Gorgon gorgon, Angelica sinensis, sophora flavescens, Radix Phellodendron, and Radix Salvia miltiorrhiza. Each tablet contained 0.52 g of the ingredients, and the participants took three tablets three times a day. The treatment course lasted six weeks, with no medication during menstruation, and the cured cases were followed up for 1 month. The Ethics Committee of the Affiliated Hospital of Liaoning University of Traditional Chinese Medicine (No. 2005L-01418) approved the study protocol, and all subjects participated voluntarily and signed informed consent.

Efficacy and Safety Measures

Effectiveness Indicators and Criteria. The primary efficacy measures were the comprehensive effect of chronic PID and the effect of dampness-heat stasis syndrome, while the secondary efficacy measures were the curative effect of local signs of chronic PID and the curative effect of main symptoms of dampness-heat stasis syndrome. The scores of chronic pelvic inflammatory signs, traditional Chinese medicine (TCM) syndrome, and local signs scores were compared before and after treatment between the two groups.

Safety Indicators and Criteria. Safety indicators and criteria included comparing changes in physical indicators and laboratory tests before and after treatment and comparing the incidence of adverse events (AEs) during the trial between the two groups.

Statistical Analysis

Statistical analysis of adverse reactions was performed using the chi-square test. The statistical analysis was carried out using SAS 8.1 software. All statistical tests were bilateral, and a P value of ≤ 0.05 was considered to indicate a statistically significant difference.

RESULTS

Enrollment and Baseline Comparison Before Treatment

A total of 480 cases were enrolled in this study, with 360 cases in the Yinghua Tablet group and 120 cases in the Fuyankang Tablet group. Among them, 466 cases completed the test, with 350 cases in the Yinghua Tablet group and 116 cases in the Fuyankang Tablet group. Fourteen cases dropped out, resulting in a dropout rate of 2.92% (2.78% in the Yinghua Tablet group and 3.33% in the Fuyankang Tablet group). There was no significant difference in the dropout rate between the groups ($P > .05$). A total of 454 cases (340 cases in the Yinghua Tablet group and 114 cases in the Fuyankang Tablet group) conformed to the protocol, accounting for 94.58% of the enrolled cases (94.44% in the Yinghua Tablet group and 95.00% in the Fuyankang Tablet group).

Demographic Comparison Before Treatment. Before treatment, the two groups had no significant differences in demographic data such as ethnicity, marital status, occupation, age, height, and weight ($P > .05$). Furthermore, there were no significant differences in vital signs, number of pregnancies, disease duration, menstruation, treatment history, history of drug allergy, comorbidities, and concomitant medication between the two groups before treatment ($P > .05$). However, contraceptive methods were statistically different between the two groups before treatment ($P < .05$). Prolonged menstruation showed statistical significance between the two groups before treatment ($P < .05$), while no statistical significance was found in other variables ($P > .05$).

Comparison of Symptom and Sign Scores. Before treatment, a comparison of symptom and sign scores, as well as traditional Chinese medicine (TCM) symptom scores, revealed a statistically significant difference between the groups ($P < .05$).

Effectiveness Analysis

Comprehensive Curative Effect of Disease. Table 1 compares clinical outcomes between the Yinghua Tablet and Fuyankang Tablet groups. The clinical recovery rate was 8.53% in the Yinghua Tablet group and 5.26% in the Fuyankang Tablet group. The markedly effective rate was 57.65% in the Yinghua Tablet group and 37.72% in the Fuyankang Tablet group. The total effective rate was 94.12% in the Yinghua Tablet group and 78.07% in the Fuyankang Tablet group. The difference between the groups was statistically significant ($P < .05$).

When comparing the markedly effective rate between the experimental and control groups, the PPS (Positive Percentage Score) of the Yinghua Tablet minus the Fuyankang Tablet was 19.93. The total effective rate of the Yinghua Tablet and Fuyankang Tablet was 16.05. These results indicate that Yinghua Tablet had a better therapeutic effect than Fuyankang Tablet.

Symptom and Sign Scores and Treatment Effectiveness. Before treatment, a comparison of the symptom and sign scores between the two groups revealed a statistically significant difference ($P < .05$). The decrease in symptom and sign scores was 14.50 ± 5.39 in the Yinghua Tablet group and 11.28 ± 6.35 in the Fuyankang Tablet group. Within each group, the decrease in scores before and after treatment was statistically significant ($P < .05$). The detailed results are presented in Table 2.

Table 1. Comprehensive Curative Effect Evaluation and Results

Grouping	Cases (n)	Clinical Healing (n, %)	Obvious Effect (n, %)	Effective (n, %)	Ineffective (n, %)	Markedly Effective Rate (n, %)	Total Effective (n, %)
Yinghua Tablet	340	29 (8.53)	167 (49.12)	124 (36.47)	20 (5.88)	196 (57.65)	320 (94.12)
Fuyankang Tablet	114	6 (5.26)	37 (32.46)	46 (40.35)	25 (21.93)	43 (37.72)	89 (78.07)
Statistics	29.301	-	-	-	-	19.93	16.05
P value	.0000	-	-	-	-	.0002	.0000

Note: Clinical Healing: the number (n) and percentage (%) of cases that achieved complete healing; *P* value: the significance level of the statistical analysis, with ".0000" indicating a highly significant difference.

Table 2. Changes in Composite Score of Disease Signs and Symptoms from Baseline to Week 6

Item	Cases (n)	Day 0	Week 6	Day 0 to Week 6	Paired *t* value	*P* value
Yinghua Tablet	340	20.98 ± 4.30	6.48 ± 4.20	14.50 ± 5.39	49.6134	.0000
Fuyankang Tablet	114	19.87 ± 4.53	8.59 ± 5.31	11.28 ± 6.35	18.979	.0000
Statistic	/	2.360	4.329	4.865	/	/
P value	/	0.0187	.0000	.0000	/	/

Note: Case Number: the number of cases in each group; Day 0: the score at baseline; Week 6: the score at 6 weeks; Day 0 to Week 6: indicates the change in score from baseline to week 6; Paired *t* value and *P* value: the statistical analysis results for the change in scores within each group.

Table 3. Changes in the Curative Effect of TCM Syndrome

Grouping	Cases (n)	Clinical Healing n(%)	Obvious effect n(%)	Effective n (%)	Ineffective n (%)	Markedly Effective Rate n(%)	Total Effective n (%)
Yinghua Tablet	340	39 (11.47)	152 (44.71)	130 (38.24)	19 (5.59)	191(56.18)	321(94.41)
Fuyankang Tablet	114	8 (7.02)	36 (31.58)	47 (41.23)	23 (20.18)	44(38.60)	91 (79.82)
Statistic		16.122				10.567	21.639
P value		.0001				.0012	.0000

Note: $P < .05$ were considered statistically significant.

Table 4. Comparison of TCM Syndrome Scores and Components from Baseline to the 6th Week.

Grouping	n (Missing)	Pre-Treatment	Post-Treatment	Pre And Post-Treatment	Paired *t* value	*P* value
Yinghua Tablet	340	15.32 ± 3.34	4.59 ± 3.31	10.73 ± 4.12	48.0314	.0000
Fuyankang Tablet	114	14.45 ± 3.33	6.22 ± 4.00	8.23 ± 4.87	18.0392	.0000
Statistic		2.409	4.309	4.931	/	/
P value		.3223	.0000	.0000	/	/

Note: The values are presented as mean ± standard deviation. The paired *t* test was used to compare each group's pre-treatment and post-treatment scores. $P < .05$ were considered statistically significant.

Table 5. Comparative Results of Local Signs, Therapeutic Effects and Components

Grouping	Cases (n)	Clinical healing n(%)	Obvious effect n(%)	Effective n(%)	Ineffective n(%)	Markedly effective rate n(%)	Total effective n(%)
Yinghua tablet	340	45 (13.24)	120 (35.29)	132 (38.82)	43(12.65)	165(48.53)	297(87.35)
Fuyankang tablet	114	12 (10.53)	33 (28.95)	40 (35.09)	29(25.44)	45(39.47)	85(74.56)
Statistic		6.197				2.816	10.469
P value		.0128				.0933	.0012

Note: $P < .05$, a statistically significant difference.

Table 6. Comparison of Changes in Scores of Local Signs from Baseline to Week 6 Between the Two Groups

Grouping	n (Missing)	Pre-Treatment	Post-Treatment	Pre-Post Treatment	Paired *t* value	*P* value
Yinghua Tablet	340	5.66 ± 1.73	1.89 ± 1.36	3.77 ± 1.97	35.2593	.0000
Fuyankang Tablet	114	5.42 ± 1.84	2.37 ± 1.76	3.05 ± 2.08	15.6570	.0000
Statistic		1.261	3.017	3.317	/	/
P value		.2078	.0027	.0010	/	/

Note: The values are expressed as mean ± standard deviation.

Table 7. Summary of Adverse Events

Item	Yinghua Tablet(n = 360)			Fuyankang Tablet(n = 120)			Fisher *P* value
	Example times	Number of cases	Incidence rate	Example times	Number of cases	Incidence rate	
Total AEs	13	13	3.61	2	2	1.67	.3767
AEs associated with investigational drugs	1	1	0.28	2	2	1.67	.1557
AEs not associated with the investigational drug	12	12	3.33	0	0	0.00	.0434
An AEs that leads to shedding	2	2	0.56	1	1	0.83	1.0000
Serious AEs	0	0	0.00	0	0	0.00	1.0000

Note: AE, Adverse Event

Effectiveness of Traditional Chinese Medicine (TCM) Syndrome Treatment. As shown in Table 3, the recovery rate for Yinghua Tablet was 11.47%, while for Fuyankang Tablet, it was 7.02%. The markedly effective rate was 56.18% for Yinghua Tablet and 38.60% for Fuyankang Tablet. The total effective rate was 94.41% for Yinghua Tablet and 79.82% for Fuyankang Tablet. The difference between the two groups was statistically significant ($P < .05$).

TCM Syndrome Score and Curative Effect. The TCM syndrome scores and the reduction in scores were 10.73 ± 4.12 for the Yinghua Tablet group and 8.23 ± 4.87 for the Fuyankang Tablet group. The difference in TCM syndrome scores between the two groups before and after treatment was statistically significant (Table 4, $P < .05$).

Curative Effect of Local Signs. The recovery rate for Yinghua Tablet was 13.24%, while it was 10.53% for Fuyankang Tablet, as presented in Table 5. The markedly effective rate of the Yinghua Tablet was 48.53%, while Fuyankang Tablet was 39.47%. There was no significant difference between the two groups ($P > .05$). The total effective rate for Yinghua Tablet was 87.35%, and Fuyankang Tablet's was 74.56%. The difference between the two groups was statistically significant ($P < .05$).

Physical Sign Score and Efficacy. The scores and reduction values of local signs in the two groups were 3.77 ± 1.97 for the Yinghua Tablet group and 3.05 ± 2.08 for the Fuyankang Tablet group. There were statistically significant differences in the scores and reduction values of local signs between the two groups before and after treatment ($P < .05$).

Safety Analysis

Following treatment, the two groups had no significant differences in vital signs ($P > .05$). Among the 360 cases in the Yinghua Tablet group, a total of 13 adverse events (AEs) occurred, representing an incidence of 3.61%. In the Fuyankang Tablet group, out of 120 cases, 2 AEs occurred, corresponding to an incidence of 1.67%. However, there was no statistically significant difference in the incidence of AEs between the two groups ($P = .3767$).

In the Yinghua Tablet group, there was 1 case with 1 AE related to the study drug, resulting in an incidence of 0.28%. In the Fuyankang Tablet group, there were 2 cases with 2 AEs related to the study drug, corresponding to an incidence of 1.67%. However, there was no statistically significant difference in the incidence of drug-related AEs between the two groups ($P = .1557$).

In the Yinghua Tablet group, there were 12 AEs unrelated to the study drug in 12 patients, representing an incidence of

3.33%. No AEs unrelated to the study drug occurred in the Fuyankang Tablet group. There was a statistically significant difference in the incidence of non-drug-related AEs between the two groups ($P = .0434$).

In the Yinghua Tablet group, 2 cases experienced adverse events leading to shedding, resulting in an incidence of 0.56%. In the Fuyankang Tablet group, 1 case had an adverse event leading to shedding, with an incidence of 0.83%. However, there was no statistically significant difference in the incidence of adverse events leading to shedding between the two groups ($P = 1.0000$).

No serious adverse events were reported in either of the two groups.

DISCUSSION

The main symptoms of chronic pelvic inflammatory disease include abdominal distension, abdominal pain, lumbosacral pain, increased leucorrhea secretion (yellow in color), severe abdominal pain during menstruation, increased menstrual volume with long duration, presence of blood clots in menstruation, fatigue, yellow urine, and dry stool. Yinghua tablets are formulated with Danshen (the root of red-rooted salvia), Kushen (*Sophora flavescens*), Pugongying (Dandelion), Yuanhu (*Corydalis yanhusuo*), Jiguanhua (*Celosia argentea*), Loulu (*Rhamnus chinensis*), and Yiyiren (Coix seed). These ingredients are known for their efficacy in promoting blood circulation, removing blood stasis, clearing heat, and eliminating dampness. Yinghua tablets have been found to be a safe and effective treatment for chronic PID.

The Yinghua tablets formula contains Salvia miltiorrhiza, which promotes blood circulation and alleviates stagnation, nourishes blood and calms the mind, relieves pain, and regulates menstruation. Bitter ginseng also has heat-clearing and detoxifying properties. Yuanhu is derived from the dried tuber of *Corydalis yanhusuo* and is known for its ability to promote blood circulation and alleviate pain. It is mainly used for various conditions caused by blood stasis. The combination of Kushen and Yuanhu in the Yinghua tablets formula enhances the blood-activating effect of Salvia miltiorrhiza and also enhances its heat-clearing and moisturizing properties.

Dandelion has been found to possess antimicrobial and anticancer properties, and it can also help in treating gastric ulcers by improving duodenal tension and enhancing its contraction. Clinically, it is believed that Dandelion has a detoxifying effect on the stomach and can help alleviate heat-related symptoms.[9] Cockscomb is known for its ability to promote blood circulation and stop diarrhea. In addition to its heat-clearing and detoxifying properties, it is also used to eliminate carbuncles and relieve swelling.[10] Coix seed is beneficial for the spleen and stomach as it helps clear excess moisture from the body. In the formula, Coix seed not only invigorates the spleen but also protects the stomach from potential side effects of other ingredients.[11,12] In conclusion, using heat-clearing and detoxifying herbs in the formula has shown positive effects in treating damp-heat stasis in chronic PID. Based on theoretical considerations, the formulation consisting of these seven medicinal herbs is safe and effective for treating chronic PID.[13,14]

In this experiment, we conducted a pharmacodynamic study on Yinghua Tablet based on the pathogenesis of PID sequelae, functional indications, mechanism of action, and the pharmacological effects of each constituent. The results demonstrated that Yinghua Tablet exhibited a significant therapeutic effect in a rat model of chronic PID induced by mixed bacterial suspension, phenol glue, and intrauterine foreign body placement. Furthermore, additional studies in a mouse model revealed that Yinghua Tablet possessed significant analgesic properties against abdominal pain induced by glacial acetic acid and exhibited pain-relieving effects against heat stimulation. In the phase III clinical study, Yinghua Tablet effectively inhibited several common pathogens in gynecology. These findings strongly support the hypothesis that Yinghua Tablet achieves its therapeutic effect in treating chronic PID through mechanisms such as promoting blood circulation, removing blood stasis, and exerting bactericidal and anti-inflammatory effects.

Study Limitations

Some limitations of this study should be acknowledged. Firstly, the study focused on the efficacy and pharmacological effects of Yinghua Tablet in treating chronic pelvic inflammatory disease, and additional investigations may be required to explore its safety profile, potential drug interactions, and long-term effects. Lastly, the study primarily assessed the effects of Yinghua Tablet on specific symptoms and pathogen inhibition, and further research is needed to understand its broader impact on overall health outcomes and quality of life in patients with chronic PID.

CONCLUSION

In conclusion, the findings of this study support the safety and efficacy of Yinghua Tablet in the treatment of chronic pelvic inflammatory disease. The observed low incidence of adverse events, further strengthens its profile as a safe treatment option. The pharmacodynamic results align with the intended functional indications of the Yinghua Tablet, providing a solid pharmacological foundation for future clinical applications and the potential expansion of its use in related conditions.

CONFLICT OF INTEREST

All authors declared The Yinghua tablets developed by SANZ Pharmaceutical Co., Ltd.

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This study did not receive any funding in any form.

ETHICS COMMITTEE APPROVAL

The study protocol was approved by the Ethics Committee of Affiliated Hospital of Liaoning University of Traditional Chinese Medicine (No. 2005L-01418).

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