

Efficacy of Si-Wu-Tang on Treating Primary Dysmenorrhea: A Systematic Review and Meta-Analysis

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ABSTRACT: According to prescriptions from famous gynecologists, Si-Wu-Tang (SWT) has been one of the main treatments for primary dysmenorrhea (PD). This systematic review and meta-analysis aim to test the efficacy and safety of SWT in treating PD. First, randomized controlled trials (RCTs) of SWT in treating PD were researched. Data were from the Year 2000 to June 2022. A cumulative meta-analysis was then performed based on those data. A total of 228 potential studies relevant to this study were searched, and 22 RCTs were included. Twenty studies compared the effect of SWT with Western medicine (WM) in treating PD. In addition, two studies compared the effect of SWT with Danggui Shaoyao San (DSS) in treating PD. The results revealed that SWT was more effective than Nonsteroidal anti-inflammatory drugs (NSAIDs), and SWT was more effective than DSS in treating PD. These results indicate that SWT might be effective in treating PD.

KEYWORDS: Transactional Medical Science; Disease Treatment and Therapies; Si-Wu-Tang; Primary Dysmenorrhea; Chinese Herbal Medicine.

■ Introduction

Background:

Dysmenorrhea refers to cyclic cramping pain in the lower abdomen of a woman's body. Symptoms of sweating, tachycardia, headaches, nausea, and vomiting are often accompanied after or during menstruation periods. Primary Dysmenorrhea (PD) is pain without significant pathological pelvic disease. Several studies have shown the prevalence of dysmenorrhea to range from 16% to 90% in populations of students, teenagers, their mothers, and other individuals from special groups like industrial workers.¹ According to a meta-analysis of 20,813 young women, 71.1% were impacted by dysmenorrhea. Within the meta-analysis, across 11,226 women, 20.1% recorded absenteeism from school due to dysmenorrhea, and a report that 40.9% of them had their class performance impaired due to dysmenorrhea.² Although pains from dysmenorrhea are not life-threatening, they can be very distractive in women's lives and activities.³

The pathogenesis of primary dysmenorrhea is unclear. However, Dawood found a positive correlation between vasoactive prostanoid secretion and primary dysmenorrhea.⁴ Therefore, Nonsteroidal anti-inflammatory drugs (NSAIDs) were the primary therapy for primary dysmenorrhea. NSAIDs are prostaglandin synthetase inhibitors (PGSIs) that can relieve the symptoms.¹ Furthermore, Owen found that significant pain was relieved by PGSIs for most women.⁵ However, some NSAIDs appeared to have side effects on women. A study showed that indomethacin was likely to cause slight gastrointestinal discomfort. Moreover, there was also a lack of sufficient evidence to prove the safety of some of the NSAIDs like flurbiprofen.⁶

Chinese Herbal Medicine (CHM) has long been used in East Asia. Currently, some Chinese herbs have already been

used to treat Primary Dysmenorrhea. The efficacy of Chinese Herbal Medicine (Danggui Shaoyao San) in treating primary dysmenorrhea has been systematically reviewed.³⁹ Compared with the placebo, CHM was significantly ($P < 0.01$) more effective in relieving pain. Moreover, within the comparison with conventional therapies (NSAIDs), CHM also showed significantly stronger effects in ($P < 0.01$) pain relief, compared with conventional therapies (NSAIDs), and its benefit could last for more than three months or more in most cases.⁷ Si-Wu-Tang (SWT) was one of the main treatments for primary dysmenorrhea, according to prescriptions from famous gynecologists.⁹ SWT is mainly composed of 4 types of herbs: prepared Rehmanniae Radix Praeparata (Shudihuang), Paeoniae Radix Alba (Baishao), Angelicae Sinensis Radix (Danggui), and Chuanxiong Rhizoma (Chuanxiong).⁴⁰ To clearly show the efficacy and safety of SWT, meta-analysis and systematic review are needed, such as the previous study on Danggui Shaoyao San for treating PD.³⁹ However, such existing studies with high statistical homogeneity were limited. Furthermore, more recent evidence and subgroup comparisons were needed to be included in the test of the SWT efficacy. Randomized Controlled Trials of SWT in treating SWT studies existed. However, there was no analysis to compare subgroups with different types of interventions. Moreover, existing meta-analyses or systematic reviews only take account of a single type of SWT, but no combination studies of different kinds of SWT are conducted. Therefore, the study's objective was to make a systematic review and meta-analysis of the efficacy and safety of SWT with the most recent studies and data. The efficacy is measured by the total effective rate of overall symptom reduction. The safety is evaluated by the adverse effect description being recorded in the study.

Abbreviations:

SWT= Si-Wu-Tang, PD= Primary Dysmenorrhea, NSAIDs= Nonsteroidal Anti-inflammatory Drugs, RR= Relative Risk, CI= Confidence Interval, RCT= Randomized Controlled Trials, PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses, TER= Total Effective Rate, PGSI= Prostaglandin Synthetase Inhibitor, DSS= Danggui Shaoyao San.

Research Method

Data Collection and Data Selection:

This study researched randomized control trials (RCTs) of Si-Wu-Tang (SWT) as a treatment for PD from the Year 2000 to June 2022. Databases were derived from PubMed, the Cochrane Library, Elsevier, China National Knowledge Infrastructure, and JSTOR.

The used terms include: (Primary dysmenorrhea OR menstruation OR menstrual pain OR menstrual disorders OR dysmenorrhea) AND (Si-Wu-Tang OR Four-agents-decoction OR Si-Wu-decoction OR Chinese Herbal Medicine OR Chinese Traditional Medicine OR Herbal Medicine) in English or Chinese.

The data was selected, and the quality of the data was assessed. This process was performed individually by the researcher. To determine the data quality, the study used the “revised Cochrane risk of bias tool for randomized trials (rob2)” to measure the risk of bias.³⁶ The following domains are being assessed: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain is rated as “low risk,” “high risk,” or “some concerns.” If the study was scored as “high risk,” it means it did not include enough information for some domains.

Criteria for inclusion in the meta-analysis:

1. The type of study was Randomized Controlled Trials (RCTs) or other quasi-RCTs. Studies written in Chinese and English would be accepted. However, case studies, case series, qualitative studies, or similar studies that cannot provide detailed information on the efficacy of SWT would be excluded.

2. All participants in the study were patients of primary dysmenorrhea.

3. The experiment interventions were SWT alone or with some additions due to the difference in the condition of patients. All kinds of formulations would be accepted. The control interventions were Western medicine, other CHM, or placebo.

4. Results of the study need to be measured by the following methods: pain level, treatment response rate, the use of other pain-reliever, or the quality of life. Therefore, data were either dichotomous or quantitative.

Data Analysis

The statistical analysis was performed using RStudio 2022.02.3+492. Since all data were either dichotomous or qualitative, relative risks and 95% confidence intervals (CIs) are used to express treatment effects. Subgroup analysis was performed based on the type of medicine, control type, or clinical heterogeneity. Risk ratio (RR) (or Relative risk) was

calculated using the ratio of patients in the experimental group that reflect treatment as effective treatment divided by the ratio of patients in the control group that reflect treatment as effective. The total effective rate (TER) recorded in the study is used to calculate the RR.

Results and Discussion

Results of the study search:

The study search results are shown in Figure 1 as a PRISMA flowchart. The search identified 228 potential study that was relevant to this study. At last, 22 studies met the inclusion criteria of this study.⁹⁻³⁰ The included types of SWT are ‘Taohong Si-Wu-Tang,’ ‘Danggui Si-Wu-Tang,’ and ‘Xiangfu Si-Wu-Tang.’

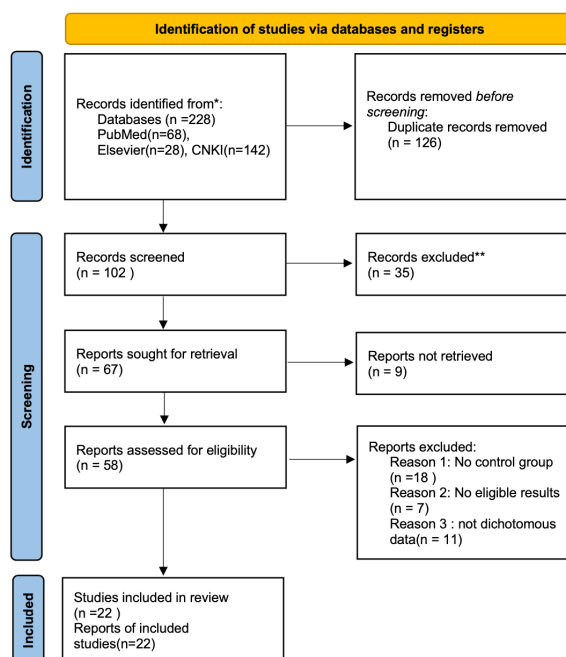


Figure 1: The flow chart of the study process. CNKI = Chinese National Knowledge Infrastructure

Risk of bias:

The overall risk of bias graph is shown in Figure 2. The risk of bias was moderate or low for most cases. However, all data were at high risk for bias due to deviations from intended interventions. The reason was that all studies did not adequately address the method of randomization or the RCTs were not conducted in a single or double-blind way.

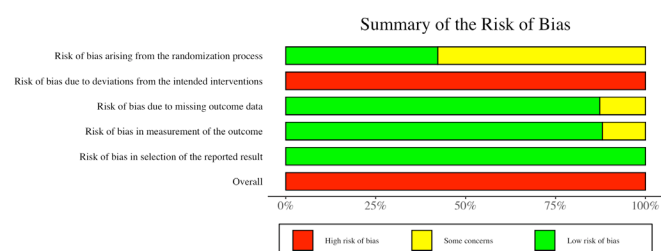


Figure 2: Summary of the Risk of Bias: author's judgment about each risk of bias domain is presented as a percentage across all studies included.

Effects of SWT

SWT vs. NSAIDs:

A total of 20 studies⁹⁻²⁸ (2275 women) compared the effects of SWT with NSAIDs (Ibuprofen, Flufenamic acid capsules, or Indomethacin). All studies reported a total effective rate (TER). In TER, the results revealed that SWT was more effective than NSAIDs (RR 2.36, 95% CI 1.92-2.92, $P < .0001$). The statistic I^2 for heterogeneity was high ($I^2 = 57.2\%$). (Figure 3)

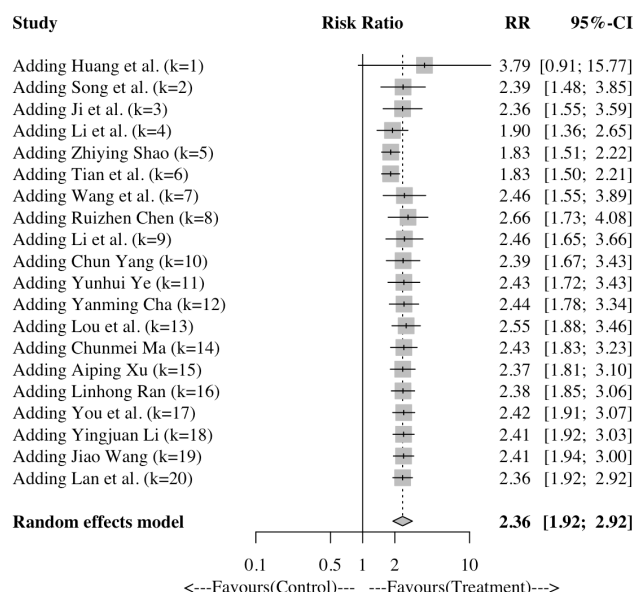


Figure 3: Forest plot of SWT vs. NSAIDs. RR = Relative Risk, CI= Confidence Interval

SWT vs. other CHM:

Two studies^{29,30} (179 women) compared the effect of SWT on Danggui Shaoyao San (DSS). Both studies reported TER and the results revealed that SWT was more effective than DSS in treating PD (RR 3.2130, 95% CI 1.9534-5.3338, $P < .0001$). The statistic I^2 for heterogeneity was low, with almost no heterogeneity ($I^2 = 0.00\%$). (Figure 4)

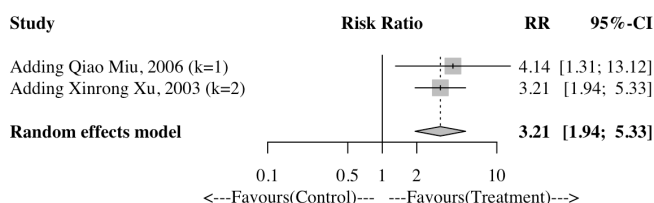


Figure 4: Forest graph for SWT vs. DSS. RR= Relative Risk, CI=Confidence Interval.

Discussion

This systematic review and meta-analysis analyzed 22 studies with 2454 women on the effect of SWT in treating PD. The results showed that SWT was more effective in treating PD than NSAIDs or DSS.

SWT and NSAIDs were compared in 20 studies. SWT was more effective in treating PD than NSAIDs (RR 2.36, 95% CI 1.92-2.92, $P < .0001$). However, the heterogeneity was high ($I^2 = 57.2\%$). According to Western medicine, the

mechanism of this disease was the enhanced contraction of the smooth muscle of the uterus and the small arteries of the myometrium, resulting in pain due to ischemia and hypoxia in the uterus. Therefore, most of the symptomatic treatment was taken to treat this disease. Currently, three major categories of drugs are recognized as major treatments for primary dysmenorrhea, namely NSAIDs, contraceptives, and calcium channel blockers, which are effective and fast, but have greater side effects, and treat the symptoms but not the root cause and are prone to recurrent attacks.³² Studies have also shown that CHM significantly improved pain relief with long-term efficacy compared to conventional therapies.⁷ Results revealed in this study also proven this statement.

According to the theory of Traditional Chinese Medicine, Si-Wu-Tang is a good formula for tonifying the blood, invigorating the blood, and regulating menstruation compared to other CHMs since it focuses more on dealing with patients with deficiency of both qi and blood symptoms.³³ Two studies compared the effect of SWT or DSS in treating PD. The results displayed a more favorable outcome toward SWT in treating PD (RR 3.2130, 95% CI 1.9534-5.3338, $P < .0001$). The heterogeneity is low ($I^2 = 0.00\%$). All those results showed the significant effect of SWT in treating PD. The pharmacology of SWT could be interpreted. In previous research, it has shown that the main component, *Semen persicae* contains aromatic cyanophoric glycoside extract that can increase the activity of cytochrome oxidase in energy metabolism and inhibit ADP-induced platelet aggregation; *Danggui* (*Angelica*) contains aromatic acids that inhibit platelet aggregation and inhibits vascular smooth muscle proliferation; *Paeonia lactiflora* composed mainly of monoterpen glycosides has vasodilatation, anti-thrombosis, anti-platelet aggregation, and inhibition of angiotensin-converting enzyme activity.³³ That information on the mechanism of SWT in treating PD would make SWT a promising safe drug for PD. Moreover, recent research has also shown that SWT inhibits oxytocin-induced uterus contraction in women.³⁴ Also, SWT improved the blood coagulation function in women, improving their quality of life.³⁵

Although this study included plenty of observations on the efficacy of SWT in treating PD, many limitations still exist. First, all data in this study were dichotomous, and all patients were Chinese. So, whether there was variability due to different regions' patients could not be determined, and the conclusion from the present study could not be applied to other areas of the world until further relevant studies confirmed it. Second, the studies included in our meta-analysis did not specifically describe the process of randomization, and the blindness of studies could not be determined. This would reduce the reliability of the study since the risk of bias due to the blinding of patients or researchers was high. Third, all data were measured in TER instead of other methods, such as pain intensity in scale. Again, this would reduce the reliability and validity of the study. A more specific pain measurement should be adopted in further studies to improve reliability.

■ Conclusion

The systematic review included 22 RCTs that showed a higher total effective rate in the SWT treatment group than in the control group being treated by NSAIDs or DSS in treating dysmenorrhea. However, this study had a high risk of bias due to the need for more description in the randomization process and blinding in all the included studies. Therefore, more reliable and detailed RCTs had to be conducted and analyzed to prove better SWT's reliability in treating PD.

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