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Efficacy and safety of Yangxinshi tablet for chronic heart failure: A systematic review and meta-analysis

Yangxinshi Tablet for Chronic Heart Failure

Abstract

BACKGROUND

The specific benefits of Yangxinshi Tablet (YXST) in the treating chronic heart failure (CHF) remain uncertain.

AIM

This study aimed to systematically evaluate the efficacy and safety of YXST in CHF treatment.

METHODS

Randomized controlled trials (RCTs) investigating YXST for CHF treatment were retrieved from eight public databases up to November 2023. Meta-analyses of the included clinical studies were conducted using Review Manager 5.3.

RESULTS

Twenty RCTs and 1845 patients were included. The meta-analysis results showed that the YXST combination group, compared to the conventional drug group, significantly increased the clinical efficacy rate by 23% (RR=1.23, 95%CI (1.17, 1.29), P<0.00001), left ventricular ejection fraction by 6.69% (MD=6.69, 95%CI (4.42, 8.95), P<0.00001) and 6-minute walk test by 49.82 m (MD=49.82, 95%CI (38.84, 60.80), P<0.00001), and reduced N-terminal pro-B-type natriuretic peptide by 1.03 ng·L^{-1} (SMD=-1.03, 95%CI (-1.32, -0.74), P<0.00001), brain natriuretic peptide by 80.95 ng·L^{-1} (MD=-80.95, 95%CI (-143.31, -18.59), P=0.01), left ventricular end-diastolic diameter by 3.92 mm (MD=-3.92, 95%CI (-5.06, -2.78), P<0.00001), and left ventricular end-systolic diameter by 4.34 mm (MD=-4.34, 95%CI (-6.22, -2.47, P<0.00001). Regarding safety, neither group reported any serious adverse events during treatment (RR=0.54, 95%CI (0.15, 1.90), P=0.33). In addition, Egger's test results indicated no significant publication bias (P=0.557).

CONCLUSION

YXST effectively improves clinical symptoms and cardiac function in patients with CHF while maintaining a favorable safety profile, suggesting its potential as a therapeutic strategy for CHF.

Key Words: Yangxinshi Tablet; Chronic heart failure; Cardiac function; Systematic evaluation; Meta-analysis

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Core Tip: Chronic heart failure represents a severe manifestation and late-stage complication of various heart diseases. This study aims to conduct a systematic evaluation of the efficacy and safety of Yangxinshi Tablet in the treating chronic heart failure through meta-analysis. The results indicate that Yangxinshi Tablet effectively improved clinical symptoms and cardiac function in patients with chronic heart failure while maintaining a favorable safety profile, suggesting its potential as a therapeutic strategy for chronic heart failure.

INTRODUCTION

Chronic heart failure (CHF) is a complex clinical syndrome characterized by ventricular systolic and/or diastolic dysfunction caused by abnormal alterations in heart structure or function. CHF is primarily characterized by weakness, dyspnea, and fluid retention resulting from impaired ventricular function and inadequate peripheral blood supply[1, 2]. Moreover, CHF represents the end-stage of various heart diseases. The condition is a significant cause of reduced quality of life and an elevated risk of mortality in patients with cardiovascular conditions. This makes CHF a critical global public health concern[3, 4]. Epidemiological data reveal that the global prevalence of CHF in adults ranges from 1% to 3% and that the incidence of CHF significantly increases with age. Studies

indicate that, on average, patients with congestive heart failure experience a heightened risk of mortality, with a survival rate of less than 50% within the first year and a more pronounced decline within 5 years[5, 6]. The incidence of CHF in China is 2.75/100,000 person-years (287/100,000 person-years in men and 261/100,000 person-years in women). Additionally, approximately, three million new cases of heart failure are recorded each year[7, 8]. The 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America Guidelines for the Management of Heart Failure recommend a baseline treatment strategy for CHF consisting of a quadruple regimen, including renin-angiotensin system inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 inhibitors[2]. Although these drugs have demonstrated beneficial effects on overall mortality, rates of rehospitalization, progression of left ventricular insufficiency, and exercise tolerance in patients with CHF, achieving satisfactory efficacy remains a challenge in some patients. Furthermore, concerns have arisen regarding adverse events associated with long-term medication[9, 10].

As research advances, an increasing number of researchers are recognizing the potential role of Chinese medicine in enhancing the prognosis of CHF[11, 12]. The treatment of CHF with traditional Chinese medicine (TCM) involves multiple components, targets, and mechanisms[13]. The Yangxinshi Tablet (养心氏片, YXST) is a kind of proprietary Chinese medicine composed of *Panax ginseng* C. A. Mey. (Renshen), *Astragalus membranaceus* (Fisch.) Bunge. (Huangqi), *Salvia miltiorrhiza* Bge. (Danshen), *Corydalis yanhusuo* W.T.Wang (Yanhusuo), *Crataegus pinnatifida* Bge (Shanzha), *Codonopsis pilosula* (Franch.) Nannf. (Dangshen), *Ganoderma lucidum* (Leyss. ex Fr.) Karst. (Lingzhi), *Pueraria lobata* (Willd.) Ohwi (Gegen), *Angelica sinensis* (Oliv.) Diels (Danggui), *Epimedium grandiflorum* Morr (Yinyanghuo), *Rehmannia glutinosa* (Gaetn.) DC (Dihuang), *Coptis chinensis* Franch (Huanglian), and *Glycyrrhizae Radix* et Rhizoma (Gancao)[14]. YXST benefits Qi (气), warms Yang (阳), activates blood circulation and reduces blood stasis. Moreover, YXST has been widely used since its development to treat CHF, coronary heart disease, myocardial infarction, depression,

and other diseases[14]. YXST was identified to inhibit myocardial fibrosis and resist ventricular remodeling by inhibiting cardiomyocyte apoptosis[15]. In patients with CHF, YXST improves cardiac function by modulating multiple metabolic pathways, including oxidative stress, energy metabolism, and fatty acid and amino acid metabolism[16]. In patients with CHF, YXST also relieves anxiety and depression and increases exercise tolerance, thereby improving quality of life[17]. This may serve as a potential treatment strategy for patients with CHF. However, owing to the lack of high-quality evidence, the specific benefits of YXST in patients with CHF remain unclear. This was a meta-analysis of randomized controlled trials (RCTs) that evaluated the efficacy of YXST for the treatment of CHF. This study aimed to provide evidence-based support for the clinical use of YXST.

MATERIALS AND METHODS

This meta-analysis is registered with PROSPERO under registration number CRD42024507360.

Search strategy

A comprehensive search was conducted in English and Chinese databases to identify all relevant clinical studies from the time of database inception to November 2023. The search was conducted using English and Chinese databases, including PubMed, Cochrane Library, Web of Science, EMBASE, China National Knowledge Infrastructure, Wanfang, VIP, and China Biomedical Literature Database. The search strategy used a combination of subject terms and free words. The subject terms used were YXST and chronic heart failure, and the free terms were supplemented by MeSH and the Cochrane Library. The search was independently conducted by authors Lu and Yu and any differences were resolved by discussion.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (i) the study was designed as a RCT. (ii) The included participants were adults (≥18 years) who met the diagnostic criteria for CHF[18]. (iii) The experimental group received YXST in combination with conventional treatment, whereas the control group received conventional treatment alone. (iv) The efficacy indicators included clinical efficacy rate, N-terminal pro-B-type natriuretic peptide (NT-proBNP), brain natriuretic peptide (BNP), left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), 6-minute walk test (6-MWT), and readmission rate. The clinical efficacy rate represented the proportion of patients with signs and symptoms of CHF in remission. The safety indicator was adverse events.

The exclusion criteria were as follows: (i) The same research results were repeatedly reported. (ii) Unavailable data.

Literature screening, data collection, and risk of bias evaluation

Literature screening, data collection, and risk-of-bias evaluation were independently performed by SH Lu and YF Yu. First, two researchers independently screened the literature using NoteExpress 3.9.0 software. Second, the two researchers independently organized and filled in the basic characteristics and data statistics tables of the included studies. Furthermore, the two researchers independently assessed the risk of bias in each study with the help of the Cochrane tools. At each step, the two researchers ensured that the results were consistent. Any disagreements that arose during this period were discussed and resolved by both researchers involved.

Data analysis

RevMan 5.3 software was used to perform the meta-analysis. Dichotomous variables were expressed as relative risk (RR) and 95% confidence interval (CI), whereas continuous variables were expressed as mean difference (MD) or standardized mean difference (SMD) with a 95%CI. When I^2 was <50%, a fixed-effects model was used to analyze the data. When I^2 was ≥50%, a sensitivity analysis was required if significant

clinical or methodological heterogeneity existed. A random-effects model was used if no significant clinical or methodological heterogeneity was detected. Results were considered statistically significant at $P<0.05$. Egger's test was used to assess publication bias, with $P>0.1$ indicating no publication bias in the results.

RESULTS

Results of literature screening

A total of 287 articles were retrieved from eight public databases. In the literature screening process, 130 duplicate articles were excluded along with 137 articles that did not conform to the research theme. Finally, 20 articles were included in this study[19-38]. The literature screening process is illustrated in Figure 1.

Basic characteristics of the included literature

Twenty clinical trials and 1845 patients were included[19-38]. Of these, 935 patients were included in the YXST combination group and 910 patients were included in the conventional drug group. The publication years of the aforementioned clinical trials ranged from 2008 to 2023, and all experimental centers were located in China. Among the 20 clinical trials, 19 (95%) followed the 2023 Focused Update of the 2021 European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure, while one trial conducted by Fan *et al* did not describe specific treatment plans[23]. One study used a YXST dosage of 0.12 g/dose[28], while two studies used a YXST dosage of 0.24 g/dose[33, 34], and the remaining studies utilized a dosage of 0.18 g/dose[19-2, 29-32, 35-36]. The frequency of administration in all studies was three times/day. The duration of the studies ranged from 1 to 48 wk. The baseline information of all experimental and control groups included in the studies was comparable. The basic characteristics of the included studies are presented in Table 1.

Risk of bias assessment

The risk of bias associated with the randomized approach was unclear in nine studies. Additionally, the risk of bias due to allocation concealment and intervention blinding was unclear in 20 studies. The risk of bias for the remaining areas was low. The risk of bias assessment is displayed in Figure 2.

Clinical efficacy rate

The meta-analysis demonstrated that the YXST combination group had a significantly increased clinical efficacy rate by 23% compared to that of the conventional drug group [RR=1.23, 95%CI (1.17, 1.29), P<0.00001] (Figure 3).

NT-proBNP and BNP

Meta-analysis demonstrated that in comparison to the conventional drug group, the YXST combination group reduced NT-proBNP by 1.03 ng·L^{-1} (SMD=-1.03, 95%CI (-1.32, -0.74), P<0.00001) and BNP by 80.95 ng·L^{-1} (MD=-80.95, 95%CI (-143.31, -18.59), P=0.01) (Figure 4).

LVEF, LVEDD and LVESD

Meta-analysis demonstrated that the YXST combination group significantly increased LVEF by 6.69% (MD=6.69, 95%CI (4.42, 8.95), P<0.00001), reduced LVEDD by 3.92 mm (MD=-3.92, 95%CI (-5.06, -2.78), P<0.00001) and LVESD by 4.34 mm (MD=-4.34, 95%CI (-6.22, -2.47), P<0.00001) compared to the conventional drug group (Figure 5).

6-MWT

Meta-analysis established that the YXST combination group significantly increased 6-MWT by 49.82 m compared to the conventional drug group (MD=49.82, 95%CI (38.84, 60.80), P<0.00001) (Figure 6).

Readmission rate

Thirteen patients in the YXST combination group and 27 in the conventional drug group were readmitted due to relapse during treatment. The readmission rate in the combined YXST group was significantly lower than that in the conventional drug group (RR=0.48, 95%CI (0.26, 0.87), *P*=0.02) (Figure 7).

Adverse events

Three patients in the YXST combination group experienced adverse events, including one case of nausea, one case of slightly dry mouth, and one case of itchy skin. Six adverse events occurred in the conventional drug group, including three cases of nausea, two cases of abdominal distension, and one case of slightly dry mouth. No significant difference was observed in adverse events between the YXST combination group and the conventional drug group (RR=0.54, 95%CI (0.15, 1.90), *P*=0.33) (Figure 8).

Heart failure with preserved ejection fraction (HFpEF) subgroup analysis

An HFpEF subgroup analysis was employed to explore the clinical efficacy of YXST in the treatment of HFpEF. The results confirmed that, compared to the conventional drug group, the YXST combination group significantly improved the clinical effective rate by 19% (RR=1.19, 95%CI (1.06, 1.33), *P*=0.003), and increased the 6-MWT by 44.61 m (MD=44.61, 95%CI (17.58, 71.65), *P*=0.001). Additionally, the YXST combination group decreased the NT-proBNP by 0.73 ng·L^{-1} (MD=-0.73, 95%CI (-0.95, -0.51), *P*<0.00001). As shown in Table 2.

Publication bias

The clinical efficacy rate was defined as the primary efficacy endpoint. Egger's test of the clinical efficacy rate demonstrated no significant publication bias (*P*=0.557) (Figure 9).

DISCUSSION

CHF is a severe manifestation or late stage of various heart diseases with high mortality and readmission rates[39]. The prevention and treatment of CHF have become a global public health concern. The pathogenesis of CHF is mainly related to ventricular remodeling. The overactivation of neuroendocrine and cytokine factors is closely related to the occurrence of ventricular remodeling. As the understanding of the pathogenesis of CHF has deepened, the treatment concept for CHF has produced a major shift from traditional cardiotonic, diuretic, and vasodilator approaches to the inhibition of excessive activation of the neuroendocrine system and ventricular remodeling[40, 41]. An increasing number of studies have demonstrated that YXST can improve coronary blood flow, alleviate symptoms, such as shortness of breath caused by myocardial ischemia, and inhibit myocardial fibrosis and ventricular remodeling through its anti-inflammatory and antioxidant properties. This suggests that YXST may serve as a complementary treatment strategy for CHF[16]. This study included 20 RCTs involving 1845 patients. This is the first systematic evaluation and meta-analysis of YXST for the treatment of CHF intending to provide evidence-based support for the clinical use of YXST.

Our findings revealed that the YXST combination group significantly improved the clinical effective rate by 23% and 6-MWT by 49.82 m compared to the conventional treatment group. This suggests that YXST effectively reduces the signs and symptoms of heart failure and enhances exercise tolerance in patients with CHF. Furthermore, the combination group of YXST reduced NT-proBNP by 1.03 ng·L^{-1} and BNP by 80.95 ng·L^{-1}, indicating its role in slowing down the progression of CHF, as BNP and NT-proBNP are important reference indexes for measuring the overall prognostic efficacy of CHF. In terms of cardiac function, the combination group of YXST significantly increased LVEF by 6.69%, reduced LVEDD by 3.92 mm, and LVESD by 4.34 mm. LVEF represents the ratio of stroke volume to the left ventricular end-diastolic volume. The parameter serves as an objective indicator of the severity of heart failure (HF). Mortality in patients with HF is closely correlated with the LVEF. Additionally, LVESD and LVEDD are indicative of the volume load on the left ventricle. Increases in LVEDD and LVESD signify cardiac

dilation and compromised ventricular compliance. Both LVEF and LVEDD reflect the extent of left ventricular remodeling. These three outcome indicators suggest that YXST improves cardiac function and reverses ventricular remodeling to a certain extent. This confirms that YXST improves the patients' clinical symptoms and cardiac function, which may be the reason for the reduction in the readmission rate.

Regarding safety endpoints, the YXST combination group exhibited an adverse event rate of 0.83% (3/361), whereas the conventional drug group had an adverse event rate of 1.69% (6/355). Adverse event rates were comparable between the two groups. This suggests that YXST has a favorable safety profile. The adverse events that occurred in both groups mainly involved gastrointestinal events. As the researchers did not identify a correlation between these adverse events and YXST, we hypothesized that they may have been caused by conventional medications such as aspirin. However, owing to the narrow study base and sample size, more studies are required to further explore the safety of YXST.

HFpEF is the most common type of CHF, accounting for more than 50% of all cases[42]. An observational study in a Western country demonstrated that the 1-year mortality rate of patients with HFpEF was 20%–29%, whereas the 5-year mortality rate was as high as 53%–74%[43]. Sodium-glucose cotransporter 2 inhibitors (SGLT2i and angiotensin receptor/neprilysin inhibitors (ARNI) are commonly used for HFpEF and they effectively improve its prognosis[18, 44]. However, apart from SGLT2i and ARNI, few beneficial drugs are available for HFpEF. The current treatment regimens are still inadequate for the management of all patients with HFpEF[45]. In this study, we evaluated the clinical efficacy of YXST in treating HFpEF. The results of the HFpEF subgroup analysis demonstrated that YXST significantly increased the clinical effective rate by 19%, 6-MWT by 44.61 m, and decreased NT-proBNP by 0.73 $ng \cdot L^{-1}$ in patients with HFpEF. This suggests that YXST can reduce clinical symptoms, enhance exercise tolerance, and improve the overall prognosis of patients with HFpEF. Therefore, we hypothesized that YXST has the potential to complement SGLT2i and ARNI in the treatment of HFpEF.

According to the TCM theory, CHF is attributed to prolonged involvement of the heart, leading to a deficiency of Yangqi and blood stasis. The key to the treatment of CHF is to benefit Qi, warm Yang, and invigorate blood circulation to eliminate blood stasis[22]. The compositional characteristics of YXST, with multiple drugs and components, determine its pharmacological mechanism of action through multitarget synergistic effects. Moreover, YXST regulates neuroendocrine and cytokine levels through various pathological and physiological pathways, thereby enhancing its effectiveness in preventing and treating CHF. A previous study has reported that *Panax ginseng* C. A. Mey. (Renshen), *Astragalus membranaceus* (Fisch.) Bunge. (Huangqi), and *Salvia miltiorrhiza* Bge. (Danshen) are the main contributors to the blood-entry components of YXST[46]. Ginsenoside Rb1 inhibits calcium ion channel activity in the cell membrane and enhances myocardial contractility. *Astragalus membranaceus* (Fisch.) Bunge. (Huangqi) is mainly composed of saponins and flavonoids. Total Astragalus saponin can increase coronary blood flow and relieve myocardial ischemia. Salvia officinalis is mainly composed of Salvia quinone/ketones and salvianolic acid components, which can reduce blood viscosity and enhance blood fluidity[46]. GAO[47] discovered that YXST could protect the myocardium at the metabolic level, mainly by regulating energy metabolism and the inflammatory immune response, thus exerting an anti-HF effect using ultra-high-performance liquid chromatography-quadrupole time-of-flight mass spectrometry coupled with principal component analysis. Owing to the limited number of mechanistic studies related to YXST, further research is required to elucidate the specific mechanisms of action of the drug.

The study has some limitations: (i) the study only included a sample size of 1845, which may result in a lack of precision in the study's findings due to insufficient statistical validity; (ii) the included studies may have potential selectivity and implementation biases, which may have reduced the confidence in the meta-analysis; (iii) the duration of each included study ranged from 1 to 48 wk, and the lack of long-term follow-up results did not confirm the long-term effects of YXST on CHF; and (iv) YXST is a common proprietary Chinese medicine that is currently being used mainly in

China, leading to the fact that the experimental centers of the published clinical trials were all in China. This meta-analysis predominantly explains the role of YXST in people of Chinese ethnicity, and how the drug works in other ethnicities is not clear. In the future, more multicenter, double-blind, stratified RCTs are needed to further investigate the effects of factors such as ethnicity and treatment duration on the clinical efficacy of YXST and to provide high-quality evidence-based confirmation of the clinical significance of the drug.

CONCLUSION

YXST effectively improves clinical symptoms and cardiac function in patients with CHF while maintaining a favorable safety profile, suggesting its potential as a therapeutic strategy for CHF.

ARTICLE HIGHLIGHTS

Research background

Chronic heart failure (CHF) is a critical global public health concern. Despite treatment guidelines recommending specific medications, challenges in efficacy and concerns about adverse events persist.

Research motivation

With the increasing recognition of Chinese medicine's potential in enhancing CHF prognosis, particularly Yangxinshi Tablet (YXST), there is a need to evaluate its benefits comprehensively through evidence-based research.

Research objectives

This meta-analysis aims to assess the efficacy and safety of YXST in treating CHF by analyzing randomized controlled trials, providing valuable insights for its clinical use and potential as a treatment strategy.

Research methods

A comprehensive search in English and Chinese databases identified relevant studies meeting inclusion criteria, focusing on outcomes such as clinical effective rate, biomarkers, cardiac function parameters, exercise tolerance, readmission rates, and adverse events.

Research results

The meta-analysis revealed that YXST had significant improvements in the clinical effective rate (RR=1.23, 95%CI (1.17, 1.29), *P*<0.00001), N-terminal pro-B-type natriuretic peptide (SMD=-1.03, 95%CI (-1.32, -0.74), *P*<0.00001), brain natriuretic peptide (MD=-80.95, 95%CI (-143.31, -18.59), *P*=0.01), left ventricular ejection fraction (MD=6.69, 95%CI (4.42, 8.95), *P*<0.00001), left ventricular end-diastolic diameter (MD=-3.92, 95%CI (-5.06, -2.78), *P*<0.00001), left ventricular end-systolic diameter (MD=-4.34, 95%CI (-6.22, -2.47, *P*<0.00001), and 6-minute walk test (MD=49.82, 95%CI (38.84, 60.80), *P*<0.00001). In terms of safety, neither of the two groups experienced any serious adverse events during the treatment (RR=0.54, 95%CI (0.15, 1.90), *P*=0.33). Egger's test suggested that the study had no significant publication bias (*P*=0.557).

Research conclusions

YXST demonstrates effectiveness in improving clinical symptoms and cardiac function in CHF patients while maintaining a favorable safety profile. These findings support its potential as a therapeutic strategy for CHF, emphasizing the need for further research and clinical application.

Research perspectives

YXST effectively improves clinical symptoms and cardiac function in patients with CHF, demonstrating a good safety profile, and is expected to be a complementary treatment for CHF. Further studies should focus on long-term effects, optimal dosages,

combination therapies, and mechanisms of action to enhance understanding and utilization of YXST in CHF management.

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