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Original Article

Qishen Taohong Granule as Adjuvant Therapy for Improving Cardiac Function and Quality of Life in Patients with Chronic Heart Failure: A Randomized Controlled Trial*

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ABSTRACT **Objective**: To confirm the improvement of cardiac function and quality of life (QoL) in patients with chronic heart failure (CHF) via Chinese medicine (CM) Qishen Taohong Granule (QTG). **Methods**: This study was a single-center, prospective, randomized, controlled clinical trial. Seventy-six patients from 27 to 84 years old diagnosed with CHF New York Heart Association (NYHA) class Ⅱ or Ⅲ in stage C were enrolled and randomly assigned at a 1:1 ratio to receive QTG or trimetazidine (TMZ), in addition to their standard medications for the treatment of CHF. The study period was 4 weeks. The primary outcomes included cardiac function evaluated by NYHA classification and left ventricular ejection fraction (LVEF), as well as QoL evaluated by CHF Integrated Chinese and Western Medicine Survival Scale (CHFQLS). The secondary outcomes included 6-min walking test (6MWT), CM syndrome score, symptom and sign scores and N-terminal pro-B-type natriuretic peptide level (NT-proBNP). All indices were measured at baseline and the end of the trial. **Results**: At the 4-week follow-up period, the effective rate according to NYHA classification in the QTG group was better than that in the TMZ group (74.29% *vs*. 54.29%, $P<0.05$). But there was no significant difference in post-treatment level of LVEF between the two groups ($P>0.05$). The CHFQLS scores improved by 13.82±6.04 *vs*. 7.49±2.28 in the QTG and TMZ groups, respectively ($P<0.05$). Subgroup analysis of the CHFQLS results showed that physiological function, role limitation and vitality were significantly higher in the QTG group than in the TMZ group (15.76±7.85 *vs*. 7.40±3.36, $P<0.05$; 16.00±8.35 *vs*. 10.53±4.64, $P<0.05$; 15.31±8.09 *vs*. 7.89±4.60, $P<0.05$). Compared with TMZ group, treatment with QTG also demonstrated superior performance with respect to 6MWT, CM syndrome, shortness of breath, fatigue, gasping, general edema and NT-proBNP level. No significant adverse reactions or adverse cardiac events occurred during treatment in either group. **Conclusion**: In addition to conventional treatments, the use of QTG as an adjuvant therapy significantly improved cardiac function and QoL in patients with CHF class Ⅱ or Ⅲ in stage C. [Registration No. ChiCTR1900022036 (retrospectively registered)]

KEYWORDS chronic heart failure, Chinese medicine, Qishen Taohong Granule, cardiac function, quality of life

Chronic heart failure (CHF) has become a disorder of epidemic proportions worldwide over the past 5 decades, as mortality from atherosclerotic cardiovascular disease has decreased dramatically, and life expectancy has increased.[1] Patients with CHF typically experience impaired quality of life (QoL).[2] Therefore, it is time for clinicians to develop innovative alternative and complementary treatments that can improve QoL for CHF patients.

Insufficient myocardial energy production and/or energy metabolism disorders are important pathogenesis factors in the development of CHF.[3] As the driving force of human biological activities, "energy"

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in modern medicine is highly analogous to "qi" in CM.[3] Previous study has found that Chinese herbal medicine with qi-invigorating effects could significantly improve the myocardial energy substances in rats with heart failure.[4] Trimetazidine (TMZ), which is known to regulate myocardial energy metabolism, is commonly used in the treatment of heart failure to optimize energy metabolism substrates and promote glucose metabolism.[5]

Prof. LIAO Jia-zhen and LIN Qian, illustrious veteran Chinese medicine (CM) doctors, concluded that the basic CM pathogenesis of CHF is the interaction of qi deficiency, blood stasis and water retention.[6] With the method of tonifying qi, promoting blood circulation by removing blood stasis and inducing diuresis to alleviate edema, they formulated Qishen Taohong Granule (芪参桃红颗粒, QTG).

QTG has been used clinically to treat CHF for a number of years and has demonstrated good clinical efficacy, but evidence from randomized, controlled trials (RCTs) are still lacking. The Chinese herbal medicines in QTG with the effects of nourishing qi and promoting blood circulation, include *Astragalus membranaceus*, *Codonopsis pilosula*, *Salvia miltiorrhiza*, *Carthamus tinctorius* and so on, which have been confirmed to improve heart failure by protecting myocardial ischemia, promoting angiogenesis, improving energy metabolism, inhibiting cardiac hypertrophy and fibrosis and reducing myocardial cell apoptosis.[7-9] In this study, we therefore investigated the effects of QTG on cardiac function and QoL in CHF patients, with TMZ used as a positive control drug.

METHODS

Diagnostic Criteria

CHF was diagnosed according to Framingham heart failure criteria.[10] Cardiac function staging referred to the American College of Cardiology and the American Heart Association (ACC/AHA) CHF staging.[11] Cardiac function grading was based on the cardiac function grading protocol of the New York Heart Association (NYHA).[12] CM syndrome identification criteria referred to "the Guiding Principle of Clinical Research on New Drugs of Traditional Chinese Medicine".[13]

Inclusion Criteria

Men and women between the ages of 18 and 84 years old who were diagnosed with CHF, classified as NYHA grade Ⅱ or Ⅲ and ACC/AHA stage C, and with the syndrome of qi deficiency, blood stasis and water retention based on CM syndrome differentiation were eligible for inclusion in this trial.

Exclusion Criteria

Patients who met any of the following criteria were excluded from this trial: (1) acute myocardial infarction, cardiogenic shock, lethal cardiac arrhythmias, cardiac tamponade, pulmonary embolism, and other severe conditions; (2) serious primary diseases of lungs, liver, kidneys, endocrine system, or hematological system; (3) pregnancy or lactation; (4) allergic constitution or allergy to multiple drugs; (5) mental illness, mental disorders, dementia or malignant tumors; (6) having taken CM (including proprietary CMs) or participated in other clinical trials in the previous 2 weeks; and (7) having incomplete clinical data.

Ethics and Trial Registration

The research was approved by the Ethics Committee of Dongfang Hospital Affiliated to Beijing University of Chinese Medicine (JDF-IRB-2017030402) and registered at www.chictr.org.cn (ChiCTR1900022036). The implementation of this study adhered to the guidelines of the Declaration of Helsinki and Tokyo for humans.

Study Design

This single-center, prospective, randomized, controlled clinical trial was conducted at Dongfang Hospital Affiliated to Beijing University of Chinese Medicine in China from March 2017 to September 2019. All of the subjects provided informed consent before the trial began.

Elimination and Termination Criteria

Patients were removed from the study if they met any of the following criteria: (1) noncompliance with research protocols; (2) dropping out during the trial; (3) failing to take drugs regularly and completing follow-up in a timely manner; (4) having serious allergic reactions or adverse reactions (ARs) or adverse cardiac events (ACEs).

Primary Outcomes

The following outcomes were collected at baseline and 4 weeks; (1) Cardiac function: (a) NYHA classification (efficiency standard: excellent: heart failure was essentially ameliorated or the NYHA

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classification increased by at least 2 levels; valid: NYHA classification increased by 1 level; invalid: NYHA classification remained the same before and after the treatment; worsened: NYHA classification decreased by at least 1 level).[13] (b) Left ventricular ejection fraction (LVEF); (2) QoL measured by the CHF Integrated Chinese and Western Medicine Survival Scale (CHFQLS).[14] The CHFQLS has a total of 39 items, which can be divided into 6 dimensions, including 17 items about physiological function, 7 items about role limitation, 5 items about vitality, 4 items about social function, 3 items about mental health, and 2 items about medical support, while the final item, about overall health satisfaction, is not included in the total score. The answer to each question was graded as 0–5 points, with higher conversion scores representing better QoL. Conversion score = (highest score possible in this field – original score)/highest score possible in this field.

Secondary Outcomes

Endpoints as follows were recorded before and after treatment: (1) 6-min walking test (6MWT); (2) CM syndrome score calculated by symptom score plus sign score; (3) symptom score: each main symptom scored as 0, 2, 4, or 6 points, or 0, 3, 6 or 9 points; each secondary symptom scored as 0, 1, 2, or 3 points; and a higher score indicating poorer condition; (4) sign score observed as blood stasis syndrome, scored as 0, 3, 6, or 9 points, with higher scores representing poorer condition; and (5) N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Safety Outcomes

ARs and ACEs were recorded during the treatment. The ACEs included acute coronary syndrome, reinterventional therapy, coronary artery bypass grafting, malignant arrhythmia, recurrent angina and severe heart failure (NYHA classification Ⅳ), stroke and death.

Sample Size Estimation

Sample size estimation was based on the results reported in the previous literature,[15] and the effective rate in the CM treatment group and the control group were 85.0% and 52.5%, respectively. Specifically, the two-tailed alpha level was 0.05, and the beta level was 0.20. According to the formula below, we calculated that 34 patients were needed for each group with a ratio of 1:1. Assuming a dropout rate of 10%, the sample size was 76.

$$n=(\mu_\alpha+\mu_\beta)^2\times 2P\times\frac{(1-P)}{(P_1-P_2)^2}$$

$$P=\frac{(P_1+P_2)}{2}$$

$\mu_\alpha=1.65$, $\mu_\beta=1.28$

Random Implementation

A random number table was used to randomly allocate 76 individuals into the QTG group (n=38) and the TMZ group (n=38).[16] The allocation sequence was kept in an opaque, sealed and stapled envelope. And the envelope was no longer used if the participant was excluded or terminated.

Intervention

All of the patients received conventional Western medicine treatment according to the Chinese guidelines published in 2014 for the diagnosis and treatment of heart failure,[17] including diuretics, angiotensin converting enzyme inhibitors (ACEIs), angiotensin Ⅱ receptor blockers (ARBs), β-receptor blockers, aldosterone-receptor blockers, etc. Moreover, patients in the QTG group were treated with QTG (9 g/pouch, twice per day) dissolved in warm water, and patients in the TMZ group were treated with a 10-mg trimetazidine dihydrochloride tablet (Beijing Wansheng Pharmaceutical Co., Ltd., 20 mg per tablet, batch No. 31610009) 3 times per day. The treatment period was 4 weeks.

The drugs for the treatment of hypertension, diabetes mellitus, dyslipidemia and other diseases could be used reasonably.

Preparation of QTG

QTG was prepared and provided by Beijing Kangrentang Pharmaceutical Co., Ltd. (Beijing, China). One dose of QTG consisted of the following: *Astragalus membranaceus* 30 g, *Codonopsis pilosula* 15 g, *Salvia miltiorrhiza* 15 g, *Semen persicae* 10 g, *Carthamus tinctorius* 10 g , *Cortex mori* 10 g, *Semen lepidii* 15 g, *Polyporus umbellatus* 15 g and *Lycopus lucidus* 15 g. These ingredients were soaked in distilled water for 30 min, boiled in water for 1 h, extracted with water twice, filtered and concentrated to a concentration of 1 g/mL, and finally processed into particles through spray drying.

Statistical Analysis

All of the data were analyzed using the SPSS

20.0 software package. Continuous data are expressed as the mean ± standard deviation ($\bar{x} \pm s$), and categorical data are expressed as percentages or frequencies. For normally distributed variables, comparisons between the QTG group and TMZ group were conducted by the independent *t*-test, and comparisons within each group were analyzed by the paired *t*-test; for nonnormally distributed variables, nonparametric tests were used. Categorical variables were analyzed using the chi-squared test or Wilcoxon's test. $P<0.05$ indicated that the difference was statistically significant, and all of the tests were two tailed.

RESULTS

Baseline Characteristics

From March 2017 to September 2019, 90 CHF patients were considered eligible. For multiple reasons, only 76 patients were enrolled in this study and assigned to the QTG group and TMZ group at a 1:1 ratio. Of the 76 patients who were included, 6 (7.8%) dropped out during the treatment. The reasons for attrition included loss to follow-up, withdrawal, adverse events (AEs) and other reasons (Figure 1). There were no significant differences in baseline characteristics between the two groups (Table 1). The QTG and TMZ groups were balanced with respect to the baseline characteristics.

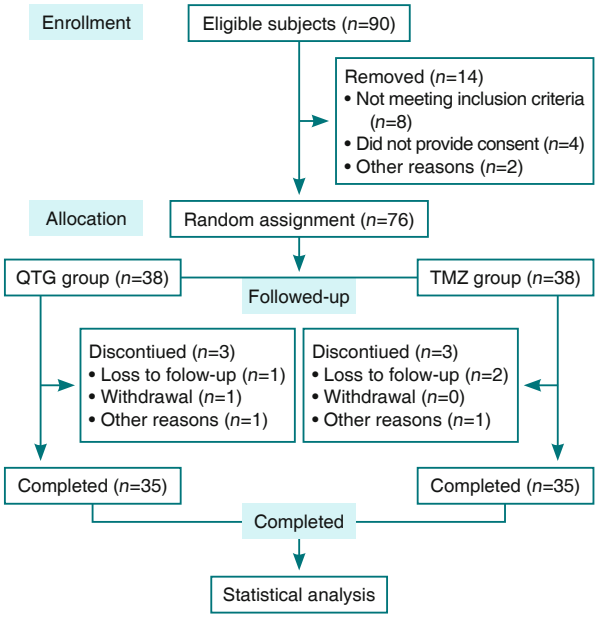

Figure 1. Flow Chart of the Study on QTG for Patients with CHF

Notes: QTG: Qishen Taohong Granule, TMZ: trimetazidine, CHF: chronic heart failure

Table 1. Baseline Characteristics of Patients with CHF

Characteristics	QTG (*n*=35)	TMZ (*n*=35)	*P* value
Demographics			
Age (Years, $\bar{x} \pm s$)	67.89 ± 10.77	67.66 ± 11.17	0.931
Male/female	24/11	20/15	0.322
Course of disease [Case (%)]			0.603
⩽1 year	13 (37.14)	9 (25.71)	
1–5 years	5 (14.29)	8 (22.86)	
⩾5 years	17 (48.57)	18 (51.43)	
Basic disease [Case (%)]			0.642
CHD[1]	24 (68.57)	27 (77.15)	
HHD	4 (11.43)	2 (5.71)	
DCM	3 (8.57)	1 (2.86)	
RHD	2 (5.71)	3 (8.57)	
PHD	1 (2.86)	2 (5.71)	
CHD[2]	1 (2.86)	0	
Medication [Case (%)]			
ACEI	17 (48.57)	19 (54.29)	0.632
ARB	17 (48.57)	16 (45.71)	0.811
Beta-blockers	25 (71.43)	28 (80.00)	0.403
Digoxin	11 (31.43)	10 (28.57)	0.794
Diuretic	25 (71.43)	29 (82.86)	0.255
Spironolactone	15 (42.86)	12 (34.29)	0.461
Primary outcomes			
NYHA classification [Case (%)]			0.553
Ⅰ	0	0	
Ⅱ	8 (22.86)	6 (17.14)	
Ⅲ	27 (77.14)	29 (82.86)	
Ⅳ	0	0	
LVEF (%, $\bar{x} \pm s$)	35.86 ± 8.18	37.31 ± 7.71	0.387
CHFQLS (Score, $\bar{x} \pm s$)			
Total score	58.84 ± 12.26	59.97 ± 11.94	0.742
Physiology	60.34 ± 14.16	62.35 ± 14.72	0.561
Role limitation	61.23 ± 13.19	60.00 ± 15.32	0.782
Vitality	56.57 ± 11.07	57.14 ± 14.95	0.595
Social function	59.86 ± 16.20	61.29 ± 12.68	0.939
Mental health	54.48 ± 21.11	56.76 ± 12.67	0.804
Medical support	48.00 ± 13.46	48.86 ± 16.05	0.619
Secondary outcomes (Score, $\bar{x} \pm s$)			
CM syndrome scores	20.17 ± 5.18	20.23 ± 4.14	0.723
Symptom or sign score			
Shortness of breath	4.00 ± 1.53	4.40 ± 1.44	0.269
Fatigue	4.06 ± 1.57	4.46 ± 1.46	0.243
Gasp	1.69 ± 0.87	1.34 ± 0.76	0.132
Palpitation	1.43 ± 1.09	1.00 ± 0.77	0.116
Chest tightness or chest pain	3.00 ± 1.78	2.86 ± 1.71	0.717

(To Be Continued)

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Characteristics	QTG (n=35)	TMZ (n=35)	P value
Blood stasis syndrome	3.43 ± 1.80	3.77 ± 1.68	0.433
General edema	1.80 ± 0.83	1.80 ± 0.83	1.000
Abdominal distention	0.77 ± 0.69	0.57 ± 0.56	0.243
6MWT (m, $\bar{x} \pm s$)	160.29 ± 56.65	180.16 ± 69.08	0.267
NT-proBNP (ng/L, $\bar{x} \pm s$)	4748.1 ± 3323.1	4657.7 ± 3611.6	0.720

Notes: CHF: chronic heart failure; CHD[1]: coronary heart disease; RHD: rheumatic heart disease; DCM: dilated cardiomyopathy; PHD: pulmonary heart disease; HHD: hypertensive heart disease; CHD[2]: congenital heart disease; 6MWT: 6-min walking test; ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin-receptor blocker; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; CHFQLS: Chronic Heart Failure Integrated Chinese and Western Medicine Survival Scale

Comparison of NYHA Functional Classification between Groups

QTG treatment significantly improved the NYHA classification by 74.29% (26/35) compared to the 54.29% (19/35) increase observed in the TMZ group (P=0.036; Table 2).

Table 2. Comparison of NYHA Functional Classification between Two Groups [Case (%)]

Group	Case	Excellent	Valid	Invalid	Worsened	Effective rate (%)
QTG	35	10 (28.57)	16 (45.72)	9 (25.71)	0	74.29*
TMZ	35	4 (11.43)	15 (42.86)	16 (45.71)	0	54.29

Notes: Effective rate was defined as the proportion of all patients who experienced an excellent or valid outcome; *P<0.05 *vs*. TMZ group

Comparison of LVEF between Groups

As shown in Figure 2, after 4 weeks of treatment, the LVEF increased to 39.94 ± 9.86 in the QTG group and 39.82 ± 7.88 in the TMZ group (all P<0.05). There was no significant difference in post-treatment level of LVEF between the two groups (P>0.05).

Comparison of CHFQLS Score in Each Group

After 4 weeks of treatment, all of the patients experienced a remarkable increase in CHFQLS score (P<0.05 for all). Specifically, there were statistically significant differences in the physiological function, role limitation and vitality scores over the duration of treatment between the two groups after treatment

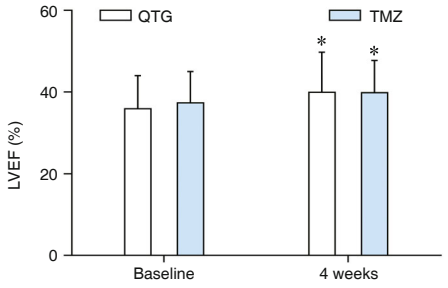

Figure 2. Comparison of LVEF between Two Groups (n=35 for each, $\bar{x} \pm s$)

Note: *P<0.05 *vs*. the same group at baseline

(all P<0.05). However, there were no significant differences in social function, mental health and medical support score after treatment between the two groups (P>0.05, Figure 3).

Comparison of CM Syndrome, Symptom and Sign Scores between Groups

Over the 4-week treatment period, there was a gradual decrease in the CM syndrome score in both the QTG (20.17 ± 5.18 to 8.80 ± 4.96) and TMZ groups (20.23 ± 4.14 to 12.66 ± 5.11). Specifically, the improvements in shortness of breath, fatigue, gasp and general edema were greater in the QTG group than in the TMZ group (P<0.05 for all). Although there were significant differences in the scores for palpitation, chest tightness or chest pain, blood stasis syndrome and abdominal distention in each group after 4 weeks of treatment, there were no significant differences in post-treatment level of these parameters between the two groups (all P>0.05, Figure 4).

Comparison of 6MWT and NT-proBNP in Each Group

As measured by the 6MWT at the end of the intervention, the walking distance of participants in the QTG group increased by 157.27 ± 65.60 m, which was greater than the increase of 107.85 ± 68.38 m in the TMZ group (P<0.05, Figure 5). As shown in Figure 5, there were improvements in the NT-proBNP levels of both groups during the process of this study; the QTG group had markedly lower NT-proBNP levels than the TMZ group after 4 weeks of treatment (P<0.05).

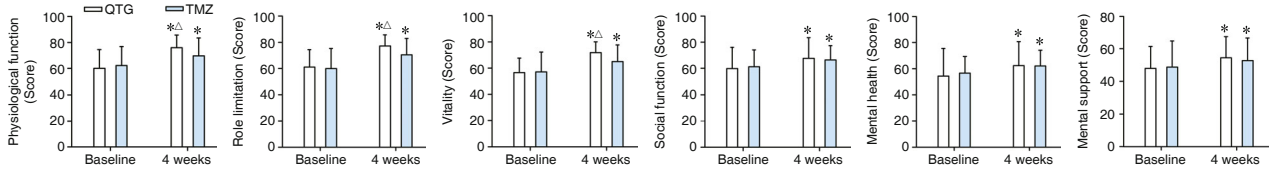

Figure 3. Comparison of CHFQLS between Two Groups (n=35 for each, $\bar{x} \pm s$)

Notes: *P<0.05 *vs*. the same group at baseline; △P<0.05 *vs*. TMZ group at the same time-points; the same below

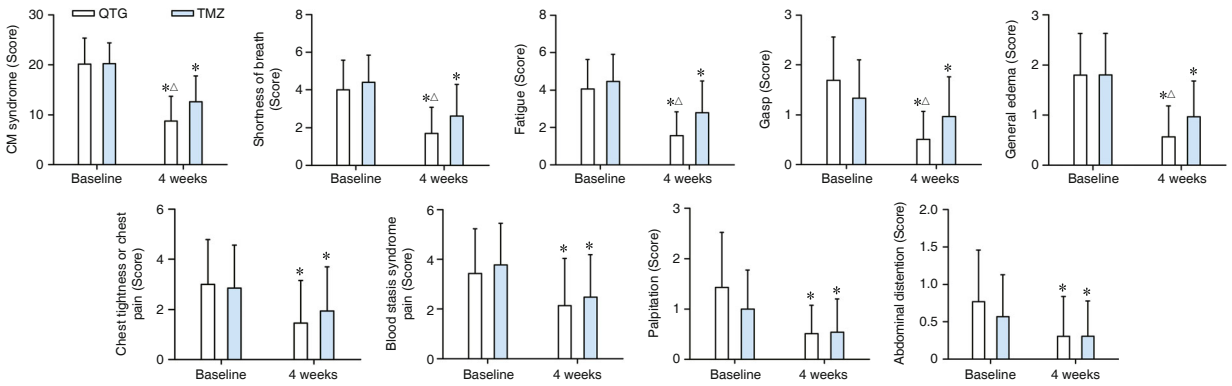

Figure 4. Comparison of the CM Syndrome, Symptom and Sign Scores between Two Groups (*n*=35 for each, $\bar{x} \pm s$)

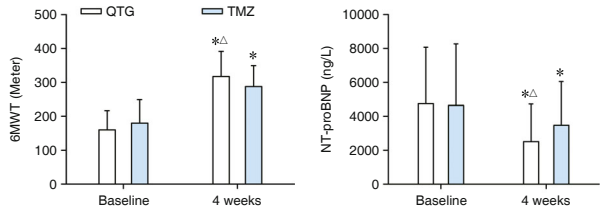

Figure 5. Comparison of 6MWT and NT-proBNP between Two Groups (*n*=35 for each, $\bar{x} \pm s$)

Safety Evaluation

No significant ARs or ACEs were reported during the treatment.

DISCUSSION

Our study demonstrated that, in the setting of CHF class Ⅱ and Ⅲ in stage C, the CM QTG enhanced cardiac function and QoL, improved exercise tolerance, CM syndrome and symptoms or signs, and decreased NT-proBNP levels.

CHF is the end stage of various cardiovascular diseases, and the 1-year mortality of severe patients is as high as 10%.[18] CM has a long history and definite curative effects for the treatment of CHF.[19] Chinese herbs, which are the most critical components of CM, are widely used in China. A variety of Chinese herbs that compose QTG have been shown to have anti-heart failure effects.[20-23]

As a simple and easy measure, NYHA classification can reflect the severity of heart failure and is related to objective indicators of exercise.[24,25] The results illustrated that QTG plus standard Western medicine therapy led to greater improvements in NYHA classification than in the TMZ group, coinciding with improved 6MWT and NT-proBNP levels. However, there were no significant differences in LVEF between the two groups after treatment, which might be related to the limited follow-up time and the small sample size. Further, it also indicated that the improvements in NYHA classification, clinical symptoms and 6MWT in patients with CHF by QTG might not be completely dependent on the improvement of cardiac pumping ability and cardiac structure.

Prolonging life and promoting QoL are the ultimate goals in the treatment of CHF.[26] Compared with the Minnesota Living with Hearth Failure Questionnaire (MLHFQ), the CHFQLS contains CM content, which is appropriate to China's national conditions and can better reflect the advantages and characteristics of CM in preventing and treating CHF, and it has good reliability and validity.[27] Therefore, the CHFQLS was used to evaluate the QoL in CHF patients before and after treatment in this study. The results showed that QTG could improve the total scores, physiological function, role limitation and vitality scores, enhancing the QoL of patients with CHF. This outcome shows that holistic adjustment is an advantage of CM in preventing and treating diseases.

The CM syndrome score system is based on CM symptoms and signs and is one of the most important and commonly used indices to evaluate the efficacy of CM in treating diseases.[28] Notably, significant differences in CM syndrome were observed between the QTG and TMZ groups in this study. The results of this study demonstrated that, compared with the TMZ group, QTG significantly improved the symptoms of qi deficiency (shortness of breath, weakness and gasp), which was the result of the intensive use of tonifying drugs. QTG significantly improved the symptoms of

water stagnation (general edema), but there was no difference in the symptoms or signs of blood stasis (palpitations, chest tightness or chest pain and blood stasis syndrome). Approximately 73% of the CHF patients included in this study had coronary heart disease as the basic disease. On the basis of full Western medical treatment with QTG or TMZ, full use of Western medicine antiplatelet drugs could significantly improve blood stasis symptoms or signs in the two groups compared to those before treatment, so on this basis, CM failed to show additional effects. Moreover, an increased follow-up time may reveal the benefits of CM treatment.

Our study had several limitations. First, the sample size was small, causing QTG to exert certain advantages in some outcomes in the treatment of CHF. Second, this study failed to assess long-term prognosis due to the limited observation period. In addition, due to the lack of quantitative indicators directly related to energy metabolism in this study, we are still unable to determine whether the improvement of qi deficiency symptoms is the same as the improvement of energy metabolism; this analysis requires further studies.

In conclusion, our study illustrated that QTG is safe and effective in improving cardiac function, QoL, exercise tolerance, CM syndrome, symptoms and signs, and NT-proBNP levels in patients with CHF class Ⅱ or Ⅲ in stage C on the basis of conventional treatment.

Conflicts of Interest

All authors declared that they had no conflicts of interest.

Author Contributions

Li Y and Lin Q designed the randomized controlled trial. Li XX drafted the manuscript. Fan ZJ, Cui J, Li D, Lin Q, Zhuang R and Yan RK performed this trial, and Li XX collected and analyzed the data. Li Y and Wu Y revised the manuscript. All authors reviewed and approved the final manuscript.

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