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Qishentaohong 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

Background: Qishentaohong Granule (QSG) is a traditional Chinese medicine (TCM) prescription for the treatment of chronic heart failure (CHF). The objective is to confirm the improvement of QSG on cardiac function and quality of life (QOL) in patients with CHF.

Methods: This is a single-center, prospective, randomized controlled clinical trial. Seventy-six patients (forty-four male and twenty-six female) from 27 to 84 years old with diagnosed CHF New York Heart Association (NYHA) class□ or □ in stage C were enrolled and randomly assigned in a 1:1 ratio to receive the QSG (9 g, twice daily) or trimetazidine (TMZ) (10 mg, thrice daily) in addition to their standard medications for the treatment of CHF. The study period was 4 weeks. The primary outcomes (cardiac function and QOL) and secondary outcomes were measured at the baseline and end of the trial.

Results: Thirty-five patients completed the study in each group. At the 4-week follow-up, the efective rate in NYHA classification in the QSG group was better than that in the TMZ group (74.29% vs. 54.29%, $P < 0.05$). Chronic heart failure integrated traditional Chinese and Western medicine survival scale (CHFQLS) scores were improved by 13.82 ± 6.04 vs. 7.49 ± 2.28 in the QSG 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 QSG 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, $P < 0.05$). Treatment with QSG also demonstrated superior performance in comparison to the TMZ with respect to 6-minute walking test (6MWT), TCM syndrome, shortness of breath, fatigue, gasp, general edema and the N-terminal pro-B-type natriuretic peptide (NT-proBNP) level. No significant adverse reactions (ARs) and adverse cardiac events (ACEs) occurred during treatment in either group.

Conclusion: In addition to conventional treatments, QSG as an adjuvant therapy significantly improved cardiac function and QOL in patients with CHF class □ or □ in stage C.

Trial registration: This trial is registered with ChiCTR, No. ChiCTR-TRC-12002857. Registered March 21, 2019. (retrospectively registered)

Introduction

Chronic heart failure (CHF) has become a disorder of epidemic proportions worldwide over the past 5 decades as mortality from atherosclerotic cardiovascular disease have dropped 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.

Professor Liao Jia-zhen and Professor Lin Qian, illustrious veteran traditional Chinese medicine (TCM) doctors, concluded that the basic pathogenesis of CHF is the interaction of qi deficiency, blood stasis and water retention [3]. With the method of tonifying qi, promoting blood circulation by removing blood stasis

and inducing diuresis to alleviate edema, they formulated Qishentaohong Granule (QSG, original name: Yiqi Huoxue Lishui prescription). QSG has obtained the national patent of China (No. 201711129837.6) and has shown satisfactory efficacy in clinic for the treatment of CHF.

In this prescription, *Astragalus membranaceus* and *Codonopsis pilosula*, as monarch medicines, can replenish the heart, spleen, lung qi and thoracic qi, which can make the blood flow smoothly. *Salvia miltiorrhize*, *Semen persicae* and *Carthamus tinctorius* can promote blood circulation to remove blood stasis so that the blood flows smoothly, qi is tonified without leaving any stagnation, and the internal organs are nurtured so that they can be used to perform normal gasification functions. *Cortex mori*, *Semen lepidii*, *Polyporus umbellatus* and *Lycopus lucidus* can play a role in inducing diuresis to alleviate edema.

Insufficient myocardial energy production and/or energy metabolism disorders are important pathogenesis in the development of CHF [4]. As the driving force of human life activities, the "energy" in modern medicine is highly analogous to the "qi" in TCM [4]. Previous studies have found that Chinese herbal medicine with qi-invigorating effect can significantly improve the myocardial energy substances ATP and PCr in rats with heart failure [5]. TMZ, which are known to regulate myocardial energy metabolism, are commonly used in the treatment of heart failure to optimize energy metabolism substrates and promote glucose metabolism [6].

In this study, we therefore investigated the effects of QSG on cardiac function and QOL in CHF patients, using TMZ as a positive control drug.

Materials And Methods

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 (Identifier: ChiCTR-TRC-12002857). 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 trail was conducted at Dongfang Hospital Affiliated to Beijing University of Chinese Medicine in China between March 2017 and September 2019. All the subjects were inpatients and gave informed consent before the trial began.

Subjects

Inclusion criteria

Men and women between the ages of 18–84 years old who have been diagnosed with CHF, classified as NYHA grade II or III and ACC/AHA stage C, and diagnosed with the syndrome of qi deficiency, blood stasis and water retention based on TCM 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, acute myocardial infarction, and other severe conditions; (2) serious primary diseases of lung, liver, kidney, endocrine system, or hematological system; (3) pregnancy or lactation; (4) allergic constitution or allergy to multiple drugs; (5) patients with mental illness, mental disorders, dementia or malignant tumor; (6) participants who have taken Chinese medicine (including proprietary Chinese medicines) or participated in other clinical trials in the past 2 weeks; and (7) patients who had incomplete clinical data.

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) ailing to take drugs regularly and completing follow-up in a timely manner; (4) serious allergic reactions or adverse reactions; or (5) patient death during follow-up.

Outcomes

Primary Outcomes

The following observation indexes were collected at baseline and 4 weeks. (1) Cardiac function: NYHA classification(Efciency standard [7]: Excellent: heart failure was essentially ameliorated or the NYHA classifcation increased by at least 2 levels; Valid: NYHA classifcation increased by 1 level; Invalid: NYHA classifcation remained the same before and afer the treatment; Worsened: NYHA classifcation decreased by at least 1 level). Left ventricular ejection fraction(LVEF); (2) QOL measured by CHFQLS [8]. 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, and the last one is overall health satisfaction, which is not included in the total score. The answer to each question was graded as 0, 1, 2, 3, 4, or 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 followed were recorded before and after treatment. (1) 6MWT; (2) TCM 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. A higher score

indicates poorer condition; (4) Sign score observed was blood stasis syndrome which scored as 0, 3, 6, or 9 points, with higher scores representing poorer condition; (5) 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

Sample size estimation was based on the result reported in the previous literature [9], and the effective rate of the Chinese medicine treatment group and the control group was 85% 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.

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

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

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

Random implementation

A random number table [10] was used to randomly allocate seventy-six individuals into the QSG group (n = 38) and the TMZ group (n = 38); then, they were coded A and B, respectively. Seventy-six opaque envelopes were used. A number between 1 and 76 was written on each envelope, and the group allocation was written inside the envelopes. The envelopes were used to randomly assign patients to groups; the envelope was no longer used if the participant was excluded or terminated.

Intervention

All patients received conventional Western treatment according to the Chinese guidelines published in 2018 for the diagnosis and treatment of heart failure [11], which includes diuretics, angiotensin converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), β-receptor blockers, aldosterone-receptor blockers, etc. Moreover, patients in the QSG group were treated with QSG (9 g/pouch, twice per day) dissolved in warm water, and patients in the TMZ group were treated with 10-mg trimetazidine dihydrochloride tablet (Beijing Wansheng Pharmaceutical Co., Ltd. (Beijing, China), 20 mg per tablet, batch number: 31610009) 3 times a 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 QSG

QSG prepared and provided by Beijing Kangrentang Pharmaceutical Co., Ltd. (Beijing, China). One dose of QSG consisted of the following: *Astragalus membranaceus* 30 grams (g), *Codonopsis pilosula* 15 g, *Salvia miltiorrhize* 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 minutes, boiled in water for 1 hour, 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 data were analyzed using the Statistical Product and Service Solutions (SPSS) 20.0 (Shanghai Cabit Information Technology Co., Ltd.) software package. Continuous data are expressed as the mean ± standard deviation (SD), and categorical data are expressed as percentages or frequencies. For normally distributed variables, comparisons between the treatment group and control group were conducted by independent t-tests, and comparisons within each group were analyzed by paired t-tests; for non-normally distributed variables, nonparametric tests were used. Categorical variables were analyzed using the chi-squared test or Wilcoxon test. $P < 0.05$ indicated that the difference was statistically significant, and all tests were two-tailed.

Results

From March 2017 to September 2019, 90 CHF patients were considered eligible. Due to multiple reasons, only 76 patients were enrolled in this study and assigned to the QSG group and TMZ group at a 1:1 ratio (QSG group n = 38; TMZ group n = 38). Of the 76 patients who were included, 6 (7.8%) dropped out during the treatment. There were no significant differences in baseline characteristics between the two groups. The reasons for attrition included loss to follow-up, withdrawal, adverse events and other reasons (Fig. 1).

Baseline characteristics

The baseline characteristics of the two groups are shown in Table 1. The QSG group and the TMZ group were balanced with respect to the baseline characteristics.

Table 1
Baseline characteristics

Characteristics	QSG (n = 35)	TMZ (n = 35)	*P* value
Demographics			
Age (Year, mean ± SD)	67.89 ± 10.77	67.66 ± 11.17	0.931
Male/Female	24/11	20/15	0.322
Course of disease [n (%)]			0.603
≤ 1 year	13 (37.14)	9 (25.71)	
1 year ~ 5 years	5 (14.29)	8 (22.86)	
≥5 years	17 (48.57)	18 (51.43)	
Basic disease [n (%)]			0.642
CHD1	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)	
CHD2	1 (2.86)	0 (0)	
Medication [n (%)]			
ACEI	17(48.57)	19(54.29)	0.632

Notes: CHF, chronic heart failure; CHD1, coronary heart disease; RHD, rheumatic heart disease; DCM, dilated cardiomyopathy; PHD, pulmonary heart disease; HHD, hypertensive heart disease; CHD2, congenital heart disease; HFpEF, heart failure with preseved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; 6MWT, 6 minutes walking test; ACEI, angiotension converting enzyme inhibitors; ARB, angiotensin-receptor blocker; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association. CHFQLS, chronic heart failure integrated traditional Chinese and Western medicine survival scale.

Characteristics	QSG (n = 35)	TMZ (n = 35)	*P* value
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 [n (%)]			0.553
	0 (0)	0 (0)	
	8 (22.86)	6 (17.14)	
	27 (77.14)	29 (82.86)	
	0 (0)	0 (0)	
LVEF (%, mean ± SD)	35.86 ± 8.18	37.31 ± 7.71	0.387
CHFQLS (Score, mean ± SD)			
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

Notes: CHF, chronic heart failure; CHD1, coronary heart disease; RHD, rheumatic heart disease; DCM, dilated cardiomyopathy; PHD, pulmonary heart disease; HHD, hypertensive heart disease; CHD2, congenital heart disease; HFpEF, heart failure with preseved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; 6MWT, 6 minutes walking test; ACEI, angiotension converting enzyme inhibitors; ARB, angiotensin-receptor blocker; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association. CHFQLS, chronic heart failure integrated traditional Chinese and Western medicine survival scale.

Characteristics	QSG (n = 35)	TMZ (n = 35)	*P* value
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			
TCM syndrome scores (Score, mean ± SD)	20.17 ± 5.18	20.23 ± 4.14	0.723
Symptom or sign score (Score, mean ± SD)			
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 ctightness or chest pain	3.00 ± 1.78	2.86 ± 1.71	0.717
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 (Meter, mean ± SD)	160.29 ± 56.65	180.16 ± 69.08	0.267
NT-proBNP (ng/L, mean ± SD)	4748.09 ± 3323.05	4657.73 ± 3611.57	0.720

Notes: CHF, chronic heart failure; CHD1, coronary heart disease; RHD, rheumatic heart disease; DCM, dilated cardiomyopathy; PHD, pulmonary heart disease; HHD, hypertensive heart disease; CHD2, congenital heart disease; HFpEF, heart failure with preseved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; 6MWT, 6 minutes walking test; ACEI, angiotension converting enzyme inhibitors; ARB, angiotensin-receptor blocker; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association. CHFQLS, chronic heart failure integrated traditional Chinese and Western medicine survival scale.

Comparison of primary outcomes in each group

NYHA functional classification

QSG treatment signifcantly improved the NYHA classifcation by 74.29% compared to the 54.29% increase observed in the TMZ group($P = 0.036 < 0.05$;Table 2).

Table 2
Comparison of the NYHA Functional Classification between the two groups [n (%)]

Group	Excellent	Valid	Invalid	Worsened	Efective rate
QSG (n = 35)	10 (28.57)	16 (45.72)	9 (25.71)	0 (0)	74.29%△
TMZ (n = 35)	4 (11.43)	15 (42.86)	16 (45.71)	0 (0)	54.29%

Note: Efective rate was defned as proportion of all patients who experienced an excellent or valid outcome; △$P < 0.05$, compared with the TMZ group.

LVEF

As shown in Table 3, the baseline LVEF was 35.86 ± 8.18 in the QSG group and 37.31 ± 7.71 in the TMZ group. After 4 weeks of treatment, the LVEF increased to 39.94 ± 9.86 in the QSG group and to 39.82 ± 7.88 in the TMZ group. There was no significant difference in post-treatment level of LVEF and change of LVEF between the two groups ($P > 0.05$).

Table 3
Comparison of LVEF between the two groups

Characteristics	QSG		*P*	TMZ		*P*	*P*
	Baseline	4 Weeks		Baseline	4 Weeks		
LVEF, %	35.86 ± 8.18	39.94 ± 9.86*	< 0.001	37.31 ± 7.71	39.82 ± 7.88*	0.002	0.865
Change, %	4.09 ± 4.82			2.51 ± 4.59			0.145

Note: Values are expressed as mean ± SD. Change = 4-week level – baseline level. * $P < 0.05$, compared with the same group at baseline. △$P < 0.05$, compared with the TMZ group at the same time-points;

CHFQLS score

The comparison of the CHFQLS scores is shown in Fig. 2. After 4 weeks of treatment, all patients experienced a remarkable increase in CHFQLS score ($P < 0.05$ for all). Specifically, there were statistically significant differences in the total score, physiological function, role limitation andvitality scores and their change over the duration of treatment between the two groups after treatment ($P < 0.05$ for all). However, there was no significant difference in social function, mental health and medical support score and the change after treatment between two groups ($P > 0.05$).

Comparison of secondary outcomes in each group

TCM syndrome, symptom and sign scores

Over the 4-week treatment period, there was a gradual decrease in the TCM syndrome score in both the QSG (20.17 ± 5.18 to 8.80 ± 4.96) and the TMZ group (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 QSG group than in the TMZ group ($P < 0.05$ for all). Although there were significant differences in the scores of palpitation, chest tightness or chest pain, blood stasis syndrome and abdominal distention in each group after 4 weeks of treatment, the changes in these parameters across the treatment were not significantly different between the groups ($P > 0.05$ for all), as shown in Fig. 3.

6MWT and NT-proBNP

As measured by the 6MWT at the end of the intervention, the walking distance of participants in the treatment group increased by 157.27 ± 65.60 m, which was higher than the increase of 107.85 ± 68.38 m in the control group ($P = 0.01$, Fig. 4a). As shown in Fig. 4b, there was improvement in the NT-proBNP levels during the process of this study; the treatment group had markedly lower NT-proBNP levels than the control group after 4 weeks of treatment ($P = 0.038$). And the change in NT-proBNP levels was significantly different between the two groups ($P = 0.394$).

Safety evaluation.

No significant ARs or ACEs were reported during the treatment, which proves that QSG is safe for clinical use.

Discussion

Our study demonstrated that in the setting of CHF class □ and □ in stage C, Chinese prescription QSG enhanced cardiac function and QOL, improved exercise tolerance, TCM 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% [12]. TCM has a long history and definite curative effect for treatment of CHF [13]. Chinese herbs, which are the most critical component of TCM, are widely used in China. The interaction of qi deficiency, blood stasis and water retention is regarded as the main pathological change in CHF according to TCM theory [3]. QSG is a Chinese prescription that enriches qi, promotes blood circulation, and removes water retention. A variety of Chinese herbs in QSG have been proven to have anti-heart failure effects [14–17].

As a simple and easy measure, NYHA can reflect the severity of heart failure and is related to objective indicators of exercise [18, 19].The results illustrated that QSG plus standard Western medicine therapy led to greater improvements in NYHA classification than the TMZ group, which coincided with improved 6MWT and NT-proBNP levels. However, there were no statistical differences in LVEF between the two groups after treatment, which might be related to limited follow-up time and the small sample size. And it also indicated that the improvement of the NYHA classification, clinical symptoms and 6MWT in patients

with CHF by QSG might not completely is dependent on the improvement of cardiac pumping ability and cardiac structure.

Prolonging life and promoting QOL is the ultimate goal in the treatment of CHF [20]. Compared with the Minnesota Living with Hearth Failure Questionnaire (MLHFQ), the CHFQLS contains TCM contents, which is appropriate to China's national conditions and can better reflect the advantages and characteristics of TCM in preventing and treating CHF, and it has good reliability and validity [21]. Therefore, the CHFQLS was used to evaluate the QOL in CHF patients before and after treatment in this study. The results show that QSG could improve the total scores, physiological function, role limitation and vitality scores, enhance QOL of patients with CHF. This shows that holistic adjustment is the advantage of TCM in preventing and treating diseases.

The TCM syndrome score system is based on the TCM symptoms and signs, and is one of the most important and commonly used indexes to evaluate the efficacy of TCM in treating diseases [22]. Notably, statistical difference in TCM syndrome was observed between the QSG and TMZ group in this study. As common symptoms of CHF, shortness of breath, weakness and gasp are closely related to qi deficiency. The results of this study demonstrated that, compared with the TMZ group, QSG significantly improved the symptoms of qi deficiency (shortness of breath, weakness and gasp), which was the result of the intensive use of tonifying drugs. The fact that TMZ did not have similar effects illustrates the complexity of the TCM symptoms of qi deficiency. On the other hand, this finding also reflects the unique advantages of enriching qi treatment for improving the symptoms of qi deficiency. As CHF progresses, qi deficiency and blood stasis occur, which cause pulse stasis and decreased nourishment of qi and blood; the stagnation of qi and blood may lead to palpitations, chest tightness or chest and blood stasis syndrome. The movement of qi and blood is not smooth, and qi cannot exert its normal gasification function, resulting in the occurrence of water stagnation symptoms, such as general edema and abdominal distention. In this study, QSG 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 CHF patients included in this study had coronary heart disease as the basic disease. On the basis of full Western medicine treatment with QSG or TMZ, full use of Western medicine antiplatelet drugs may significantly improve blood stasis symptoms or signs in the two groups compared to those before treatment, so on this basis, TCM failed to show additional effects. Moreover, an increased follow-up time may reveal the benefits of TCM treatment.

Limitations Of The Study

Our study has several limitations. First, the sample size is small, which makes QSG show certain advantages in some outcomes in the treatment of CHF, but there were no significant differences between the two groups. 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.

Conclusion

Our study illustrated that QSG were safe and efficacious in improving cardiac function, QOL, exercise tolerance, TCM syndrome, symptoms, signs, and NT-proBNP levels in patients with CHF class or in stage C on the base of conventional treatment.

Abbreviations

ACEs, adverse cardiac events; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blocker; ARs, Adverse reactions; CHF, chronic heart failure; CHFQLS, chronic heart failure integrated traditional Chinese and Western medicine survival scale; CHD1, coronary heart disease; CHD2, congenital heart disease; DCM, dilated cardiomyopathy; HHD, hypertensive heart disease; HFpEF, heart failure with preseved ejection fraction; HFrEF, Heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; 6MWT, 6-minute walking test; MLHFQ, Minnesota Living with Hearth Failure Questionnaire; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PHD, pulmonary heart disease; QSG, Qishentaohong granule; QOL, quality of Life; RHD, rheumatic heart disease; TCM, traditional Chinese medicine; TMZ, trimetazidine.

Declarations

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All participants provided written informed consent and the protocol was approved by the Ethics Committee of Dongfang Hospital Affiliated to Beijing University of Chinese Medicine (JDF-IRB-2017030402). The implementation of this study adhered to the guidelines of the Declaration of Helsinki and Tokyo for humans.

Consent for publication

Not applicable.

Conflicting interest

All authors declared that they had no confling interest.

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Authors' contributions

Yan Li and Qian Lin designed the expriment. Xing-xing Li drafted the manuscript. Zongjing Fan, Jie Cui, Quan Lin and Rong-kunYan performed this expreiment, and Xing-xing Li collected and analyzed the data.Yan Li and Yang Wu revised the manuscript. All authors reviewed and approved the final manuscript.

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Figures

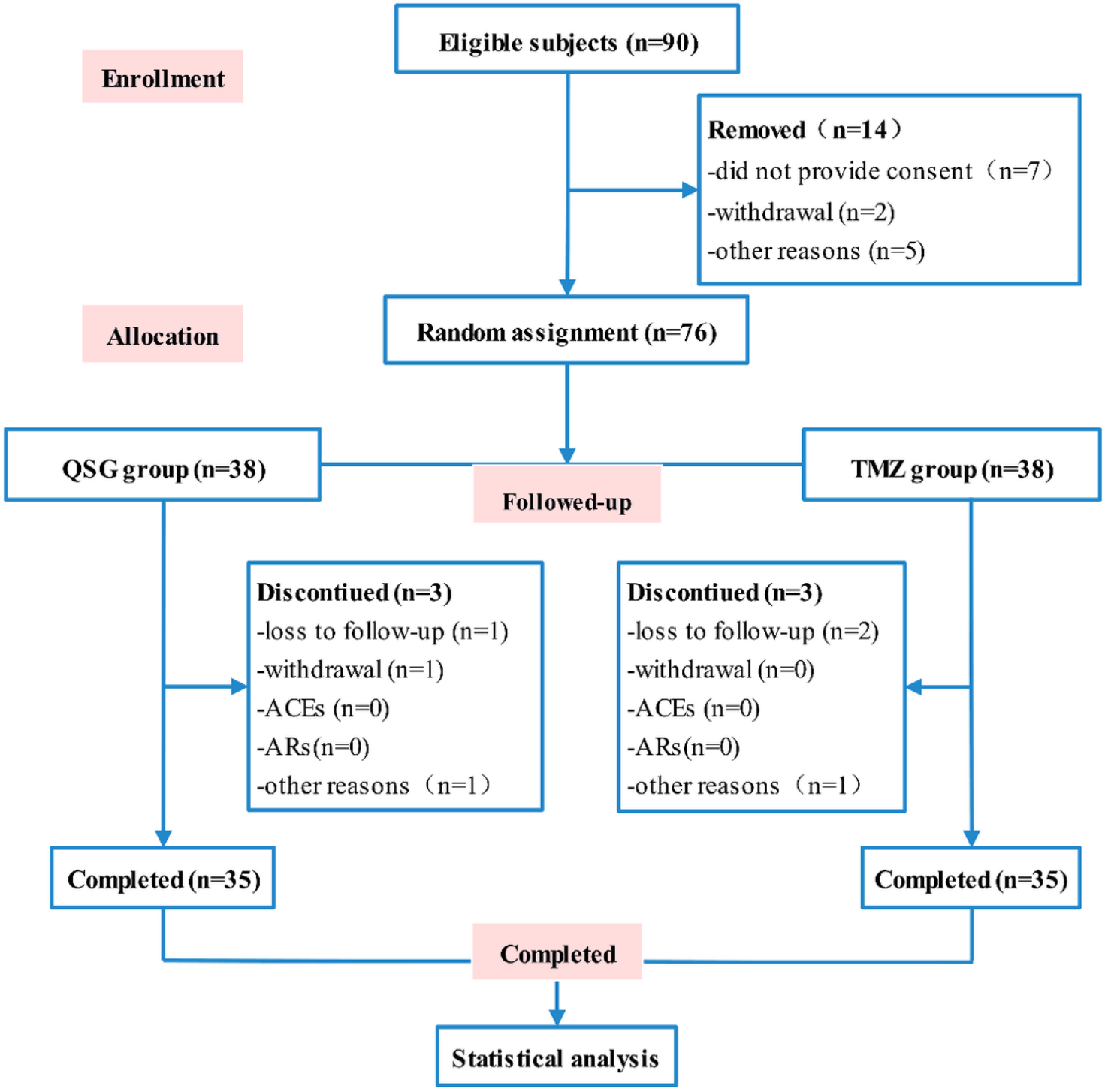
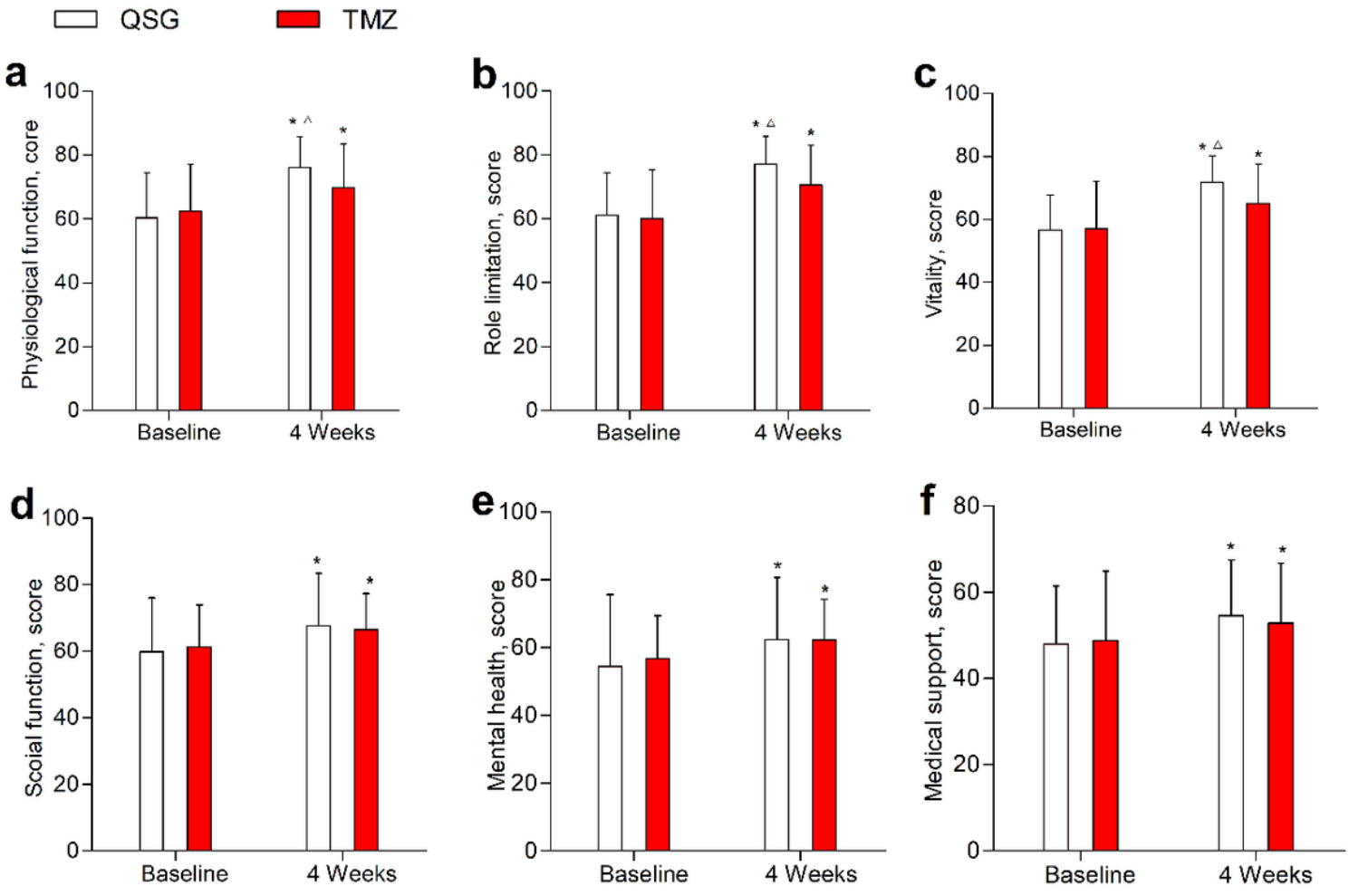


Figure 1

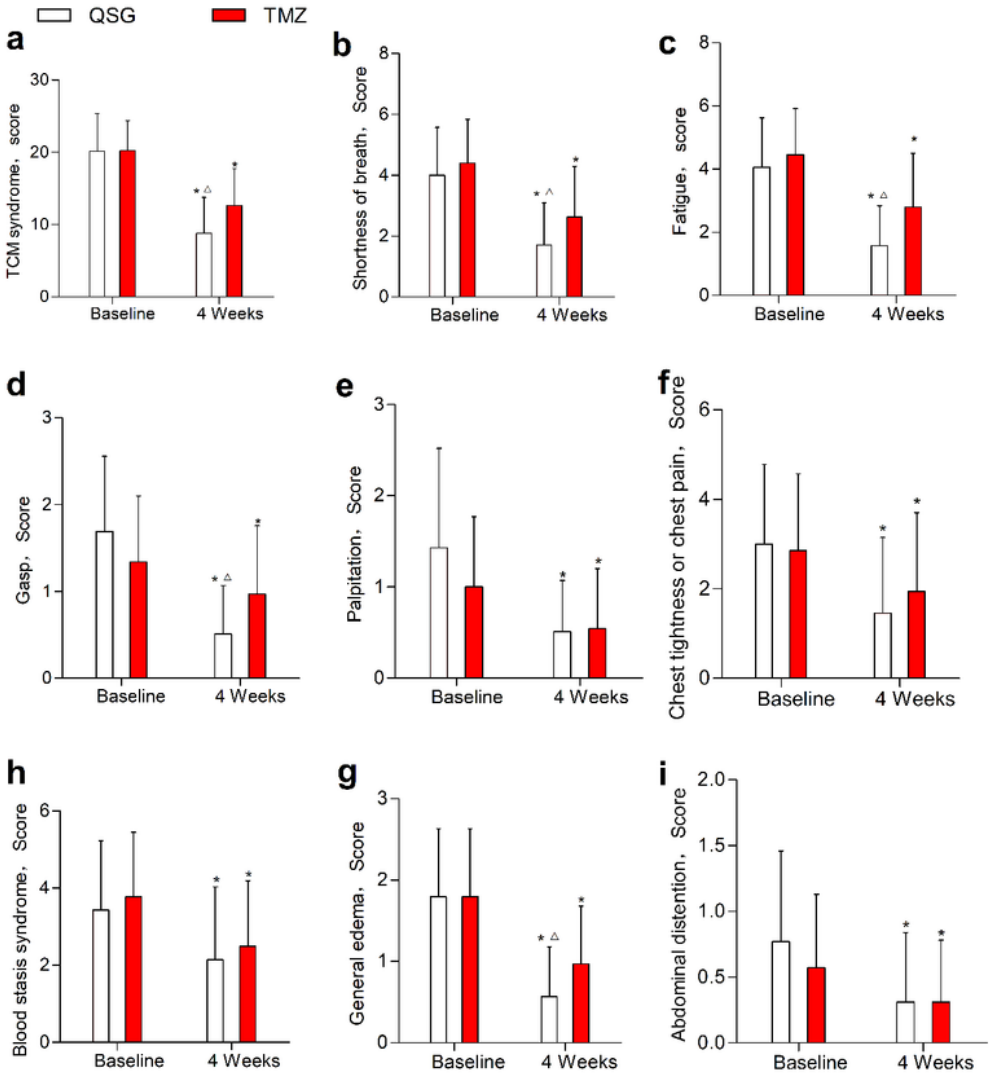
Flow chart of the study Note: QSG, Qishentaohong Granule; TMZ, trimetazidine; ACEs, adverse cardiac events; ARs, Adverse reactions.



Characteristics (Score)	QSG			TMZ		
	Baseline	4 Weeks	Change	Baseline	4 Weeks	Change
Total score	58.84±12.26	72.66±8.97*△	13.82±6.04△	59.97±11.94	67.46±10.63*	7.49±2.28
Physiological function	60.34±14.16	76.10±9.62*△	15.76±7.85△	62.35±14.72	69.75±13.77*	7.40±3.36
Role limitation	61.23±13.19	77.22±8.64*△	16.00±8.35△	60.00±15.32	70.53±12.45*	10.53±4.64
Vitality	56.57±11.07	71.89±8.26*△	15.31±8.09△	57.14±14.95	65.03±12.67*	7.89±4.60
Social function	59.86±16.20	67.71±15.69*	7.86±6.22	61.29±12.68	66.57±10.83*	5.29±5.14
Mental health	54.48±21.11	62.48±18.23*	8.00±10.94	56.76±12.67	62.29±11.98*	5.52±6.36
Medical support	48.00±13.46	54.57±12.91*	6.57±7.65	48.86±16.05	52.86±13.84*	4.00±16.51

Figure 2

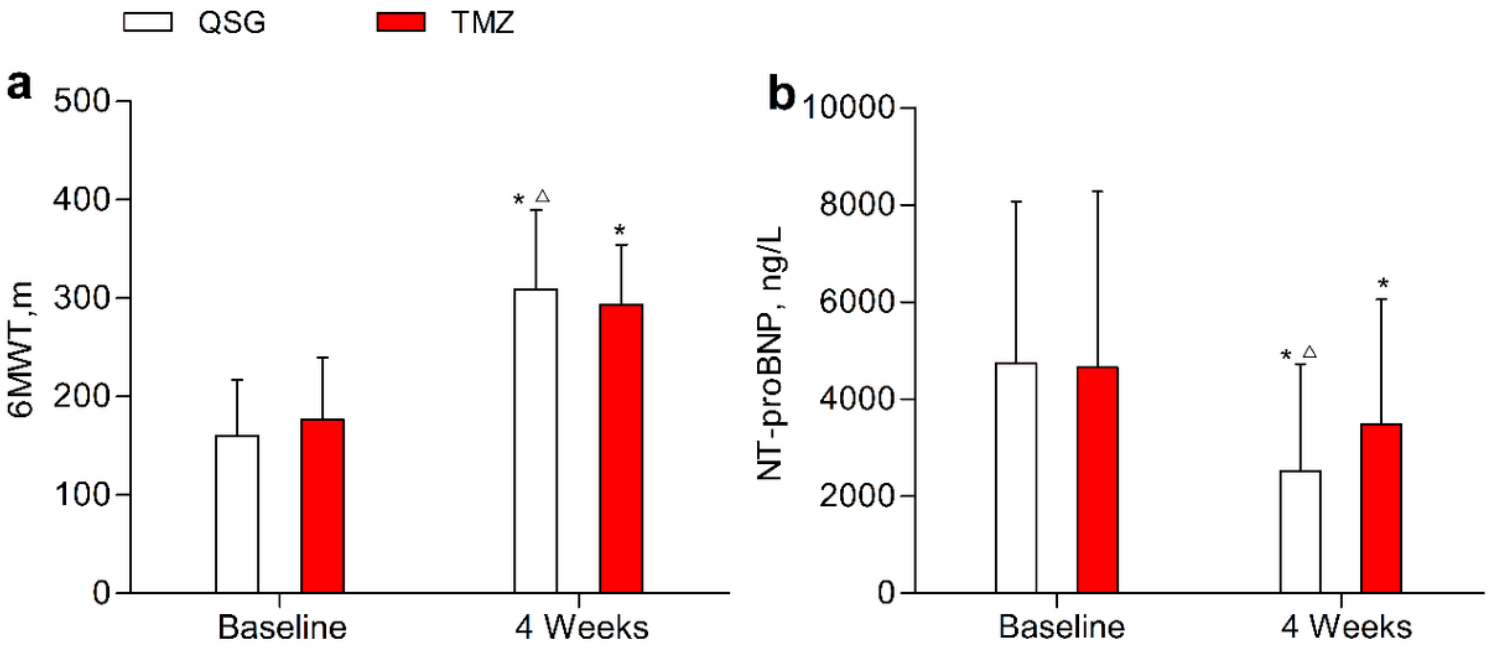
Comparison of the CHFQLS total scores and scores of each dimension between the two groups Note: Values are expressed as mean ± SD. Change= 4-week level – baseline level *P<0.05, compared with the same group at baseline; △P<0.05, compared with the TMZ group at the same time-points.



Characteristics (Score)	QSG			TMZ		
	Baseline	4 Weeks	Reduction	Baseline	4 Weeks	Reduction
TCM syndrome score	20.17±5.18	8.80±4.96*△	11.37±5.25△	20.23±4.14	12.66±5.11*	7.57±4.47
Symptoms or signs						
Shortness of breath	4.00±1.57	1.71±1.38*△	2.49±1.76	4.40±1.44	2.63±1.66*	1.66±1.57
Fatigue	4.06±1.57	1.57±1.27*△	2.49±1.76	4.46±1.46	2.80±1.69*	1.66±1.57
Gasp	1.69±0.87	0.51±0.56*△	0.46±0.66△	1.34±0.76	0.97±0.79*	0.26±0.66
Palpitation	1.43±1.09	0.51±0.56*	0.91±1.09	1.00±0.77	0.54±0.66*	0.46±0.78
Chest tightness or chest pain	3.00±1.78	1.46±1.69*	1.54±1.69	2.86±1.71	1.94±1.76*	0.94±1.59
Blood stasis syndrome	3.43±1.80	2.14±1.89*	1.29±1.82	3.77±1.68	2.49±1.70*	1.29±1.82
General edema	1.80±0.83	0.57±0.61*△	1.23±0.81△	1.80±0.83	0.97±0.71*	0.83±0.86
Abdominal distention	0.77±0.69	0.31±0.53*	0.46±0.66	0.57±0.56	0.31±0.47*	0.26±0.66

Figure 3

Comparison of the TCM syndrome, symptom and sign scores between the two groups Note: Values are expressed as mean ± SD. Reduction=4-week level – baseline level. * P<0.05, compared with the same group at baseline; △P<0.05, compared with the TMZ group at the same time-points. 6MWT and NT-proBNP



Characteristics	QSG			TMZ			P
	Baseline	4 Weeks	P	Baseline	4 Weeks	P	
6MWT, m	160.29±56.65	317.56±74.15*△	< 0.001	180.16±69.08	288.01±61.66*	< 0.001	0.01
Change, m	157.27±65.60△			107.85±68.38			0.003
NT-proBNP, ng/L	4748.09± 3323.05	2522.76± 2196.40*△	< 0.001	4657.73± 3611.57	3476.49± 2578.64*	< 0.001	0.039
Reduction, ng/L	2225.32±2317.01△			1181.24±1650.56			0.021

Figure 4

Comparison of the 6MWT and NT-proBNP between the two groups Note: Values are expressed as mean ± SD. Reduction=baseline level – 4-week level; Change= 4-week level – baseline level. *P<0.05, compared with the same group at baseline; △P<0.05, compared with the control group at the same time-points.