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Original Article

Effect of heart failure reversal treatment as add-on therapy in patients with chronic heart failure: A randomized, open-label study☆

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ABSTRACT

Objectives: The present study was designed to evaluate effect of heart failure reversal therapy (HFRT) using herbal procedure (*panchakarma*) and allied therapies, as add-on to standard CHF treatment (SCT) in chronic heart failure (CHF) patients.

Methods: This open-label, randomized study conducted in CHF patients (aged: 25–65 years, ejection fraction: 30–65%), had 3-phases: 1-week screening, 6-week treatment (randomized [1:1] to HFRT + SCT or SCT-alone) and follow-up (12-week). Twice weekly HFRT (60–75 min) consisting of *snehana* (external oleation), *swedana* (passive heat therapy), *hrudaydhara* (concoction dripping treatment) and *basti* (enema) was administered. Primary endpoints included evaluation of change in metabolic equivalents of task (MET) and peak oxygen uptake (VO_{2peak}) from baseline, at end of 6-week treatment and follow-up at week-18 (non-parametric rank ANCOVA analysis). Safety and quality of life (QoL) was assessed.

Results: Seventy CHF patients ($n = 35$, each treatment-arm; mean [SD] age: 53.0 [8.6], 80% men) were enrolled in the study. All patients completed treatment phase. Add-on HFRT caused a significant increase in METs (least square mean difference [LSMD], 6-week: 1.536, $p = 0.0002$; 18-week: −1.254, $p = 0.0089$) and VO_{2peak} (LSMD, 6-week: −5.52, $p = 0.0002$; 18-week: −4.517, $p = 0.0089$) as compared with SCT-alone. Results were suggestive of improved functional capacity in patients with HFRT (QoL; Mean [SD] HFRT + SCT vs. SCT-alone; 6-week: −0.44 [0.34] vs. −0.06 [0.25], $p < 0.0001$ and 18-week: −0.53 [0.35] vs. −0.29 [0.26], $p = 0.0013$). Seven treatment-emergent adverse events (mild severity) were reported in HFRT-arm.

Conclusion: Findings of this study highlight therapeutic efficacy of add-on HFRT vs. SCT-alone in CHF patients. The non-invasive HFRT showed no safety concerns.

What is already known?

- Current CHF management guidelines recommend evidence-based treatment and care-modalities. Moreover, there is an emphasis on patient rehabilitation that acknowledge the need for improvement in patient health-related outcome. Add-on therapies based on Ayurveda and/or herbal treatment are known to have the potential to address this lacunae.

What this study adds?

- Present study introduces HFRT, an add-on therapy to SCT that shows promising results for better CHF management.

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Abbreviations: 2D-ECHO, two dimensional-echocardiogram; ACE, angiotensin converting enzyme; ANCOVA, analysis of covariance; ARBs, angiotensin receptor blockers; CHF, chronic heart failure; DPP, double pressure product; ECG, electrocardiography; EF, ejection fraction; FAS, Full Analysis Set; IHD, Ischemic Heart Disease; HFRT, heart failure reversal therapy; HRR, heart rate recovery; LSMD, least square mean difference; MET, metabolic equivalents of tasks; NYHA, New York Heart Association; PLBS, post lunch blood sugar; PP, Per Protocol Set; QoL, quality of life; SAS, statistical analysis system; SCT, standard CHF treatment; SD, standard deviation; SHS, sampurna hruyday shudhikaran; SS, Safety Set; TEAEs, treatment emergent adverse events; TOI, time to onset of ischemia; VO_{2peak}, peak oxygen uptake.

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1. Introduction

The management of chronic heart failure (CHF) is a topic, broadly discussed since eons, and has well-established treatment regimens emphasizing the goal of reduction in symptoms and improvement of prognosis. The worldwide growing prevalence of CHF shows an annual incidence of 0.5–1.8 million in India.[1] As a result, plethora of research is performed to identify newer therapeutic targets for better management of CHF.[2] A contemporary physician is mindful of crucial objective of maximizing function in everyday life and strives to achieve the highest level of quality of life (QoL) within the limitations imposed by the disease. Along with symptoms of CHF, an array of undesirable emotions including fear and anxiety of health status lead to deterioration in the patient's morale and a progressive decline in QoL. Despite improvement in therapeutic drugs and devices, CHF has poor prognosis. The critical therapeutic advantages are those that maintain and stabilize the patient's limited functional abilities and, also improve the comfort of the patient for remaining life-span.[3]

The standard CHF treatment (SCT) includes β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), digoxin, anti-platelets and diuretics.[4] However, majority of CHF patients require complex management due to growing age, comorbidities, multiple medications, and depression or reduced coping skills.[5] Considering these exigencies, a search is ongoing for preferably non-invasive add-on therapies with SCT. Historical data have reported that β-blockers, ARBs have antioxidant, and/or anti-inflammatory properties, which may attribute to their therapeutic effects.[6,7] Several herbs are known to possess antioxidant, anti-inflammatory, antiplatelet or hypolipidemic properties.[8–14] It would, therefore, be interesting to explore if these herbs have an additional cardioprotective effect in CHF patients.

Ayurvedic physicians advocate use of conventional treatment in the acute disease phase and in chronic condition subsequent use of panchakarma therapy (a 5-step procedure for internal purification of the body) as an add-on, for providing maximum benefit to the patient.[15] Heart failure reversal therapy (HFRT) formerly known, sampurna hruyday shudhikaran (SHS) therapy is a combination of herbal treatment with panchakarma and allied therapies.[16–18] The techniques used in panchakarma namely snehana (massage), swedana (fomentation therapy) and basti (type of enema) are known to eliminate toxins.[15,19]

The primary objective of this randomized, open-label, comparative study was to evaluate the effect of HFRT as an add-on therapy to SCT on metabolic equivalents of tasks (METs) and peak oxygen uptake (VO_{2peak}) in CHF patients. The effect on ejection fraction (EF), time to onset of ischemia (TOI), double pressure product (DPP), heart rate recovery (HRR) and quality of life (QoL) were also evaluated.

2. Methods

2.1. Study population

Study participants included patients (both gender, aged 25–65 years) with CHF (New York Heart Association, NYHA Class I–III), history of CHF irrespective of angioplasty and coronary artery bypass graft on SCT, having MET values: 3–7 (inclusive), and EF between 30–65% (inclusive) on a standard two dimensional-Echocardiogram (2D-ECHO) test (6 months prior to screening). Additional inclusion criteria were systolic blood pressure not >150 mmHg and diastolic blood pressure not >90 mmHg, hemoglobin levels ≥10 g/dL, blood sugar level (fasting not <60 mg/dL and PLBS not >250 mg/dL).

Patients with suspected hypersensitivity to study therapy, acute heart failure, decompensated heart failure attack (last 3-months), irritable bowel syndrome, bleeding piles or fistula (grade-I or II piles), 2nd/3rd degree hemorrhoids, asthma or chronic obstructive pulmonary disease, abnormal thyroid function test, hepatic or renal insufficiency, cancer, physical disability (any form) leading to immobilization, participation in another study 30-days prior to screening were excluded. Patients not on stable dose of SCT (last 3-months), needing upward dose titration were excluded and also pregnant or lactating women.

The Independent Ethics Committee approved the protocol. The study was conducted in accordance with the ethical principles in the Declaration of Helsinki, consistent Good Clinical Practices, and applicable regulatory requirements. All patients or their legally acceptable representatives provided written informed consent to participate in the study.

2.2. Study design

Open-label, randomized study, conducted from 2014 to 2015 in outpatients at two centers (Bhaktivedanta Hospital, Mumbai and Shree Saibaba Heart Institute and Research Center, Nasik) was divided into 3-phases: screening (up to 1-week), treatment (6-week) and follow-up phase (12-week). At treatment phase, patients enrolled after screening were randomized (1:1) to either groups: (1) HFRT, twice/week plus SCT (like β-blockers, ACE inhibitors, digoxin, anti-platelets and diuretics) or (2) SCT-alone. Randomized and treated patients were evaluated at end of the treatment (6-week) and at 18-week in the follow phase (Fig. 1).

Permuted block randomization was performed to allot either treatment: HFRT + SCT or SCT-alone based on next available number as per the randomization chart.

2.3. Study therapy

The HFRT, a 4-step procedure *(snehana, swedana, hrudaydhara, basti)* requiring 65–75 min was performed after a light breakfast (Fig. 2; Supplementary material[15,19]).

2.4. Study evaluations

2.4.1. Cardiac function measures

Primary endpoints were improvement in MET and VO_{2peak} as evaluated by cardiac stress test with modified Bruce protocol and 12-lead electrocardiography (ECG) at baseline, 6 and 18-week. MET is ratio of metabolic rate (the rate of energy consumption) during a specific physical activity to a reference metabolic rate (3.5 ml O_2 kg^{-1} min^{-1}). VO_{2peak} is the measurement of the volume of oxygen that the body can utilize during physical exertion (VO_{2max} = MET value × 3.6).

Secondary endpoints (monitored at 6 and 18-week) included improvement in QoL: assessed by questionnaires (adapted from validated questionnaires[20–23]), EF, improvement in TOI and DPP and HRR as assessed by monitoring heart rate.

HRR is time taken to return to normal heart rate at end of stress test. TOI (time to onset 1 mm of ST segment change in more than 2 leads) and DPP (product of maximum heart rate and systolic blood pressure) were recorded during stress test.

2.4.2. Safety and tolerability

Safety was assessed throughout the study and evaluated by frequency, severity and intensity of treatment-emergent adverse events (TEAEs), serious TEAEs, physical examinations, vital signs and laboratory tests (biochemistry, hematology, and urine analysis).

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