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 ($V_{O2}$ peak) 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 $V_{O2}$ peak (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.

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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. As a result, plethora of research is performed to identify newer therapeutic targets for better management of CHF. 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.

The standard CHF treatment (SCT) includes β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), digoxin, anti-platelets and diuretics. However, majority of CHF patients require complex management due to growing age, comorbidities, multiple medications, and depression or reduced coping skills. 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.

Several herbs are known to possess antioxidant, anti-inflammatory, antiplatelet or hypolipidemic properties. 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. Heart failure reversal therapy (HFRT) formerly known, sampurna hruyday shudhikaran (SHS) therapy is a combination of herbal treatment with panchakarma and allied therapies. The techniques used in panchakarma namely snehana (massage), swedana (fomentation therapy) and basti (type of enema) are known to eliminate toxins.

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 ($V_{O2peak}$) 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, hruydaydhara, basti) requiring 65–75 min was performed after a light breakfast (Fig. 2; Supplementary material).

2.4. Study evaluations

2.4.1. Cardiac function measures

Primary endpoints were improvement in MET and $V_{O2peak}$ 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$^{-1}$). $V_{O2peak}$ is the measurement of the volume of oxygen that the body can utilize during physical exertion ($V_{O2max}$ = MET value $\times$ 3.6).

Secondary endpoints (monitored at 6 and 18-week) included improvement in QoL: assessed by questionnaires (adapted from validated questionnaires), EF, improvement in TOI and DPP (product of maximum heart rate and systolic blood pressure) were recorded during stress test.

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).
2.5. Statistical methods

2.5.1. Analysis set

Analysis sets were as follows: Safety Set (SS) randomized patients who received treatment at least once; Full Analysis Set (FAS) – patients who had primary efficacy parameters assessed post-baseline; Per Protocol Set (PP) – patients who completed the study with no protocol deviations.

2.5.2. Sample size determination

The sample size \( N = 27 \), each treatment group) was pre-specified to the minimal detectable differences of 1.5 in MET and 3.0 in \( \text{VO}_2\text{peak} \) levels (mean change from baseline) between the two treatment groups at week 12 with 80% power and a 0.05, two-sided significance level and standard deviation of 1.9 in MET and 3.8 in \( \text{VO}_2\text{peak} \) levels. Assuming 20% dropout rate, 35 CHF patients were required to be enrolled in each group.

2.5.3. Statistical analyses

Demographic and baseline characteristics of SS were summarized descriptively. The mean change in efficacy endpoints between groups was analyzed using non-parametric rank analysis of covariance (ANCOVA), with baseline values as covariates. Wilcoxon Rank Sum test was used to compare QoL data. Statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc., USA).

3. Results

3.1. Study population

Total 70/76 screened CHF patients were enrolled and randomized in open-label treatment-phase to either groups: HFRT + SCT \( n = 35 \), 50%) or SCT-alone \( n = 35 \), 50%). The study population (mean [SD] age: 53.0 [8.6]) comprised of 80% men (HFRT + SCT group, \( n = 27 \) [77%]; SCT-alone group, \( n = 29 \) [83%]). The baseline
demographic and clinical characteristics were comparable between the groups (Table 1).

All randomized patients completed the 6-week treatment-phase in both groups. A total of 34 (97%) patients in HFRT + SCT and 30 (86%) in SCT-alone group completed the follow-up (Fig. 1).

### 3.2. Efficacy measurements

Efficacy parameters were analyzed at 6 and 18-week. Patients in HFRT + SCT group showed significant improvement in MET and VO_{2peak} values from baseline, at 6-week (least square mean difference [LSMD], MET: −1.536, p = 0.0002; VO_{2peak}: −5.52, p = 0.0002) and 18-week (LSMD, MET: −1.254, p = 0.0089; VO_{2peak}: −4.517, p = 0.0089) as compared to SCT-alone group. The percent improvement in these features, sleep pattern, memory and routine could not be a reliable measure. This explains the erratic HRR profile vs. SCT-alone.

The CHF patients experience a progressive decline in QoL as their ability to perform routine physical activities is compromised due to early onset of dyspnea and fatigue. Exercise training is known to substantially increase VO_{2peak} and MET and is currently recommended to improve QoL in these patients as they become more tolerant to exertion, experience less fatigue and dyspnea and become comfortable in performing routine activities. The significantly enhanced QoL post HFRT reflected a remarkable improvement in these features, sleep pattern, memory and routine lifestyle. The 4-elements of the HFRT treatment: Snehana, Swedana, Hrudaydhara and Basti mostly act in cohesion to alleviate the detrimental effects of CHF. The improvement in QoL with HFRT treatment requires further investigation. HRR is an effective prognosis parameter at constant workload and MET-value. In this study, workload and MET-values were variable and hence, HRR could not be a reliable measure. This explains the erratic HRR results obtained in both arms of the study.

Although this study had a small sample size, there was 100% compliance in both treatment arms and the protocol deviations could not be a reliable measure. This explains the erratic HRR profile vs. SCT-alone.
were observed. The HFRT therapy augments the beneficial effects of SCT thereby improving the exercise tolerance, aerobic capacity, prognosis and QoL of CHF patients. Hence, the non-invasive HFRT therapy can be a viable option for planning the modus operandi for better CHF management.

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**Conflicts of interest**

Dr. RM is an employee of Vaidya Sane Ayurved Labs Pvt. Ltd. Drs. RS, AA and AP has received honoraria from Vaidya Sane Ayurved Labs Pvt. Ltd.

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**Appendix A. Supplementary data**

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ihj.2016.10.012.

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### Table 2

**Analysis of change from baseline in study parameters (Full Analysis Set).**

| Parameters | HFRT + SCT | SCT alone | LS Mean Change between groups<sup>a</sup> | ANCOVA p-value | Non-parametric rank ANCOVA p-value |
|------------|------------|-----------|--------------------------------|----------------|----------------------------------|
|            | LS Mean CFB (SE) | 95% CI     | LS Mean CFB (SE) | 95% CI     |                                  |
| Week-6     | N = 34      | N = 33    |                              |               |                                  |
| METs       | 2.33 (0.27) | 1.78, 2.88| 0.79 (0.28) | 0.23, 1.35 | -1.54                           |
|            | 2.86 (1.00) | 0.85, 4.86| -5.52                       | -3.84, -2.70 |
| TOI        | 200.41 (21.09) | 158.29, 242.54 | 103.21 (21.41) | 60.45, 145.97 | -97.20 |
|            | 1977.51 (604.1) | 770.68, 3184.35 | -264.89 (613.24) | -1489.98, 960.20 | 2242.40 |
| DPP        | 24.25 (16.48) | -8.67, 57.17| -24.29 (16.73) | -57.70, 9.13 | -48.54 |
| HRR        | 264.89 (613.24) | 1489.98, 960.20 | 2242.40 | 9671.76, 517.65 | -95.46, -1.62 |
| QoL        | Mean (SD) | -0.06 (0.25) | Mean (SD) | -0.06 (0.25) |                  |
|            | N = 30      | N = 30    |                              |               |                                  |
| Week-18    | N = 34      | N = 30    |                              |               |                                  |
| METs       | 2.63 (0.32) | 2.0, 3.27 | 1.38 (0.34) | 0.70, 2.05 | -1.25 |
|            | 4.96 (1.22) | 2.53, 7.40 | -4.52 | -7.86, -1.18 | 0.0089 |
| TOI        | 3.28 (0.48) | 2.33, 4.24 | 0.08 (0.51) | 0.94, 1.10 | -3.21 |
|            | 194.68 (25.34) | 144.01, 245.35 | 134.73 (26.98) | 80.78, 188.68 | -59.95 |
| DPP        | 2236.71 (807.92) | 621.17, 3852.24 | 247.33 (860.49) | -1246.33, 2194.99 | -1762.38 |
| HRR        | 26.87 (15.6) | -4.33, 58.07 | 18.55 (16.61) | -14.67, 51.77 | -8.33 |
| QoL        | Mean (SD) | 0.06 (0.25) | Mean (SD) | -0.06 (0.25) |                  |
|            | N = 30      | N = 30    |                              |               |                                  |

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<sup>a</sup> LS Mean change between groups is calculated as SCT-alone – HFRT + SCT.

ANCOVA, analysis of covariance; CFB, change from baseline; CI, confidence interval; DPP, double pressure product; HRR, heart rate recovery; HFRT, heart failure reversal therapy; LS mean, least square mean, MET, metabolic equivalents of task; QoL, quality of life; TOI, time to ischemic onset; VO<sub>2</sub>peak, peak oxygen uptake.

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### Table 3

**Treatment-emergent adverse events (Safety Set).**

| Parameters | HFRT + SCT | SCT alone | Number of patients | n (%) | n (%) |
|------------|------------|-----------|--------------------|-------|-------|
|            | N = 35     | N = 35    |                    |       |       |
| Number of patients | 5 (14.3) | 2 (5.7) |
| With at least one TEAE | 0 | 2 (5.7) |
| With at least one severe TEAE | 0 | 2 (5.7) |
| With at least one serious TEAE | 0 | 2 (5.7) |
| TEAEs      |            |           | Lower respiratory tract infection | 1 (2.9) | 0 |
|            |            |           | Upper respiratory tract infection | 1 (2.9) | 0 |
|            |            |           | Pain in cubital fossa | 1 (2.9) | 0 |
|            |            |           | Dengue fever | 1 (2.9) | 0 |
|            |            |           | Chest pain | 1 (2.9) | 0 |
|            |            |           | Cough | 0 | 1 (2.9) |
|            |            |           | Hemoptysis | 0 | 1 (2.9) |
|            |            |           | Breathlessness | 0 | 1 (2.9) |
|            |            |           | Breathlessness secondary to cardio-myopathy with left | 0 | 1 (2.9) |
|            |            |           | ventricular failure | 0 | 1 (2.9) |
|            |            |           | Dysphagia | 0 | 1 (2.9) |
|            |            |           | Elevated hypertension | 0 | 1 (2.9) |
|            |            |           | Vertigo | 0 | 1 (2.9) |
|            |            |           | Weakness | 1 (2.9) | 0 |
|            |            |           | Serious TEAE | 0 | 1 (2.9) |

HFRT, heart failure reversal therapy; SCI, standard chronic heart failure treatment; TEAE, treatment-emergent adverse event.
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