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To Evaluate the Efficacy of Heart Failure Reversal Therapy Using NT-Probnp Levels in Patients with Chronic Heart Failure

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Abstract: Heart failure is considered as a life-threatening epidemic disorder affecting about 26 million world's population and associated with considerable morbidity, mortality and healthcare expenses. Despite the availability of a range of advanced treatments and sophisticated therapies the prevalence of heart failure represents a herculean challenge. To address the challenge, the current investigation was conducted by evaluating the efficacy of Heart Failure Reversal Therapy (HFRT) in reducing left ventricular distress by assessing N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in congestive heart failure (CHF) patients. Total 76 CHF patients with NYHA Class II and III were screened from March to May 2017 and 15 CHF patients with NT-proBNP = 300-1500 pg/ml were selected for the study. NT-proBNP is measured as a marker, the value of which increases with an increase in severity of CHF. The study therapy, HFRT comprises of traditional procedure of panchkarma that includes snehana (external oleation), swedana (passive heat therapy), hrudaydhara (concoction dripping treatment) and basti (medicated enema) was administered twice daily for 7 days. Post-HFRT, ARJ kadha was administered for next 12 weeks follow-up. NT-proBNP levels were measured after a follow-up period of 90 days along with some other parameters like BMI, VO_{2peak} (evaluated by cardiac stress test with modified Bruce protocol) and weight. The findings of the investigation revealed significant reduction in NT-proBNP levels (42.46%, p = 0.009), weight (4.82%, p = 0.0007) and BMI (3.67%, p = 0.034) at the end of the follow-up period. The study also yielded significant improvements in VO_{2peak} (50.96%, p = 0.004). The overall results suggest that HFRT can possibly be explored as add-on therapy or a feasible alternative for the effective management of CHF.

Keywords: NT-proBNP, Chronic Heart Failure, Heart Failure Reversal Therapy

1. Introduction

Chronic Heart Failure (CHF) is a prevalent systemic disease affecting a significant proportion of the population worldwide. [1] Recently published INTER-CHF prospective cohort study reported India has 23% annual mortality rate owing to CHF alone. [2] Pioneering research studies have led to a change in the classic approach and development of new therapies which have ameliorated symptoms and improved the survival rate of patients with CHF. However, this chronic condition continues to remain a progressive disease causing incremental morbidity and early mortality. [3].

Owing to these exigencies, Heart Failure Reversal Therapy (HFRT), an Ayurvedic non-invasive therapy was designed to assist better survival outcomes in patients with heart failure. A randomized control trial has shown HFRT to be efficacious and safe in CHF patients with 30-65% ejection fraction (EF). [4] Another HFRT study (article in press) confirmed its effect at 90 days follow-up in CHF patients with reduced EF.

Along with development in the treatment of CHF, it is equally important to have good diagnostic markers. Good diagnostic markers help in analysis of efficacy of treatment and/or disease progression etc. Recently, measurement of circulating levels of brain natriuretic peptide (BNP), a biologically active peptide of 32 amino acids with natriuretic properties, has become a potential diagnostic aid to identify patients with heart failure. [5, 6].

Upon secretion of BNP in response to left ventricular

distress, proBNP (1-108) in cardiomyocytes is cleaved into the active hormone BNP (77-108) and inactive (1-76) N-terminal proBNP (NT-proBNP) [7]. As NT-proBNP has better stability, both in circulating blood and after sampling, it is considered to be an ideal marker for the detection and evaluation of chronic heart failure [7], pro-BNP levels are known to increase with an increase in the severity of CHF.

The main objective of this study was to evaluate the efficacy of HFRT in reducing left ventricular distress as assessed by NT-proBNP levels.

2. Materials and Methods

2.1. Study Population

CHF patients (male/female and aged between 40-70 yrs.) were screened from March to May 2017. Patients willing to participate in the study and belonging to New York Heart Association (NYHA) Class II and III with NT-proBNP levels = 300-1500 pg/ml were included in the study.

2.2. Study Protocol

At the baseline visit, all patients were examined by a physician, and the following information was obtained: medical history, including medications used; physical examination with measurements of height and weight; resting blood pressure; heart rate; and NYHA classification based on patient information. Patient then underwent study therapy i.e. HFRT and were followed up for a period of 90 days post-HFRT.

2.3. Study Therapy

HFRT is a therapeutic Ayurvedic treatment consisting of four major steps of Snehana, Sweden, Hrudaydhara, and Basti followed in the same order [4]. This procedure is performed twice in a day on patients with CHF for 7 consecutive days by trained and skilled staff. Along with HFRT, ARJ kadha (decoction of *T. arjuna, A. calamus and B. diffusa*) is also administered to the patient.

The current study included in the manuscript was conducted in accordance with the ethical principles of the Declaration of Helsinki, and all patients provided written informed consent.

2.4. Study Parameters

2.4.1. Primary Endpoint

NT-proBNP levels were measured before HFRT and after a follow-up period of 90 days. Venous blood was drawn into EDTA tubes and promptly centrifuged, and plasma was frozen at −80°C until analysis of NT-proBNP was carried out. NT-proBNP was measured by a One-Step Test for NT-proBNP Colloidal Gold assay (Mex Biotech Hongkong Ltd).

2.4.2. Secondary Endpoints

Clinical status of the patients was assessed by evaluating improvements in VO_{2peak} using cardiac stress test with modified Bruce protocol, and metabolic equivalents (METs)

after and before follow-up period. MET is the 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}). [8] VO_{2peak} is the measurement of the volume of oxygen that the body can utilize during physical exertion (VO_{2peak} = MET value × 3.6). [9] Additionally, EF was also evaluated.

2.4.3. Statistical Analysis

Normally distributed variable values are expressed as mean (SD). Other continuous variables are given as median and range. Differences in means between groups were compared using the t-test or an F test as appropriate, and differences in medians by the Mann–Whitney U test. All statistical analyses were done using Statistical Package for the Social Sciences (SPSS version 21.0).

3. Results

Seventy-six patients with CHF were screened during the study timeline and fifteen patients who were eligible according to the study screening protocol were enrolled. All the patients were successfully administered the study therapy.

Out of the fifteen patients with CHF, thirteen were males and the average age of the study population is 54.8 years (Table 1). A reduction in weight (4.82%, p = 0.0007) and BMI (3.67%, p = 0.034) was observed 90 days post-HFRT.

Table 1. *Demographic and Clinical characteristics of patients with CHF.*

Parameter	Before HFRT
Age (yrs.)	54.8±7.57
Male	12
Female	3
Weight (Kgs)	64.54±9.8
BMI (kg/m²)	24.45±2.61

There was a 42.46% reduction in NT-proBNP levels which is statistically significant (p = 0.009). Figure 1 shows the decrease in NT-proBNP levels post-HFRT therapy.
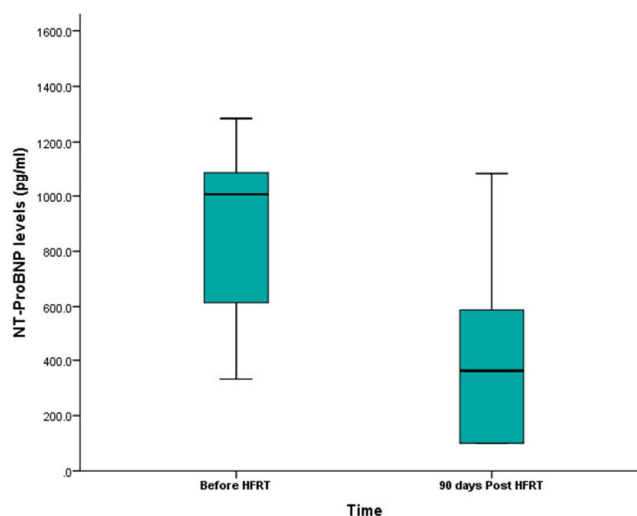

Figure 1. *Reduction in NT-ProBNP levels.*

Table 2 shows the pre- and post-HFRT values for VO_{2peak}, MET and EF. The study result shows a significant increase in VO_{2peak} levels (50.96%, p = 0.004). It hereby depicts an improvement in oxygen uptake capacity of the heart. However, the EF did not change significantly.

Table 2. *Change in the levels of study parameters at 90 days of follow up post HFRT as compared with baseline.*

Parameter	Before HFRT	90 days post-HFRT
NT-proBNP (pg/ml)	858.47±320.84	494.07±468.65 (p=0.009)
Metabolic Equivalent	4.88±2.12	7.37±1.71 (p=0.001)
VO_{2peak}	17.09±7.41	25.80±5.99 (p=0.001)
Ejection Fraction	49.92±11.61	48.69±10.74

$VO_{2peak:}$ peak oxygen uptake.

The conventional drug dosage (namely ACE –inhibitors, anti-platelets, beta-blockers, calcium channel blockers and diuretics) used before HFRT was substantially lowered 90 days post-HFRT (Table 3).

Table 3. *Concomitant medicine tapering post HFRT.*

Concomitant medicines	Before HFRT (%)	90 days post-HFRT (%)
ACE inhibitor	33.3	0
Anti-platelet	83.3	73.3
Beta blocker	60.0	53.3
Calcium channel blocker	26.6	20.0
Diuretics		
Thiazide	6.7	6.7
Loop	6.7	0
Potassium-sparing c	26.7	26.7
Pyridine-sulfonyl urea type loop	33.3	26.7
Others	43.0	34.6

ACE: Angiotensin converting enzyme.

4. Discussion

The important outcome as per our study result is the sustained efficacy of HFRT post 90 days of therapy administration. HFRT has been reported earlier [4] to be helpful in CHF patients but results of this study report its effect post 90 days using NT-proBNP as a diagnostic marker.

There has been a lot of literature published for the utility of NT-proBNP as a diagnostic marker in CHF patients. As a result, there is now growing evidence that among the BNPs, NT-proBNP is more accurate in reflecting myocardial wall tension. [10–14] Therefore, it is not only helpful in differentiating patients with normal LVEF and impaired LVEF but also a predictive diagnostic marker for HF and reduced survival at 10 years. [15] PARADIGM-HF trial even reports patients with a significant reduction in NT-proBNP had a lower subsequent rate of cardiovascular death or HF hospitalization. [16].

However, it has to be noted there is no single cut-off value depicting normal NT-proBNP level but an age-wise cut-off such as 450 pg/mL for<50 years, 900 pg/ml for 50–75 years and 1,800 pg/mL for >75 years can be considered. [17] In the

present study wherein, the mean age of the study population is about 55 years, a change in NT-proBNP levels from approximately 1000 pg/mL to 370 pg/ml, ninety days post-HFRT is remarkable. This reduction in NT-proBNP levels shows the improvement in heart functioning of the study population thereby reflecting the beneficial effect of HFRT. Furthermore, there is a reduction in conventional treatment drug dosage observed post-HFRT thereby underlining its value as an add-on therapy.

5. Conclusion

In contrast to the ample amount of literature showing the efficacy of Chinese and other alternative therapies in patients with CHF there is paucity of evidence-based studies in Ayurveda. This study is the best amalgamation of diagnostic science and Ayurveda. The results of present study reflect benefits of an wholesome Ayurvedic treatment in patients with CHF with a follow-up of 90 days. Although the study population is small, the results show promising hope for the role of Ayurveda based alternative medicine in aiding CHF patients. Therefore, more studies and/or rigorously designed RCTs are warranted to establish the efficacy of HFRT as an add-on to the conventional treatment.

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Disclosures

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