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Original Article

The effect of multiple micronutrient supplementation on quality of life in patients with symptomatic heart failure secondary to ischemic heart disease: a prospective case series clinical study

Ang-Peng Wong[1], Abdul-Latiff Mohamed[1], Aleksandra Niedzwiecki[2]

[1]Department of Graduate Studies, Research and Commercialization, Cyberjaya University College of Medical Sciences, Selangor, Malaysia; [2]Dr. Rath Research Institute, Santa Clara, CA 95050, USA

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Abstract: Heart failure is a progressive cardiovascular disorder and, in most cases, begins with atherosclerosis and ischemic heart disease. The prognosis of patients with heart failure is poor, even with improvement on the management of all forms of ischemic heart disease. There have been studies on heart failure using a single nutrient or a combination of multiple nutrients. Results are mixed. The aim of this study was to assess the influence of multiple micronutrient supplementation using the quality of life measure on patients with heart failure secondary to ischemic heart disease. This prospective case series followed 12 patients for a period between 3 to 8 months, using the Minnesota Living with Heart Failure Questionnaire (MLHFQ) as the sole outcome measure. The primary outcome was a score change over time between the start and endpoint of treatment. Change in MLHFQ mean total score was 27.08 ± 20.43 and mean symptoms score was 4.67 ± 3.34. Paired t-test showed a difference between baseline and endpoint of treatment ($P < 0.001$), which was statistically significant. A high dose of multiple micronutrients may have beneficial effects on cardiac function in patients with symptomatic heart failure. This study indicates the need for long-term controlled studies to test the efficacy and safety of this economic approach in managing heart failure.

Keywords: Heart failure, ischemic heart disease, Minnesota Living with Heart Failure Questionnaire, New York Heart Association, micronutrients

Introduction

Ischemic heart disease (IHD) is a condition where the heart can no longer pump enough blood to the rest of the body due to coronary artery disease (CAD). The narrowing of the coronary arteries due to atheromatous plaque gradually builds up over a few decades, and often results in myocardial infarction (MI) and heart failure (HF). The clinical presentations of IHD are stable angina, unstable angina, MI, arrhythmia, HF, or sudden death. HF is a progressive disorder with a loss of functioning of cardiac myocytes, resulting in a decline in the pumping capacity of the heart. CAD, IHD, and HF are closely associated, and these diseases are seen as sequential progression.

Patients with IHD and HF are often treated with angiotensin-converting enzyme inhibitors, beta-blockers, calcium channel blockers, nitrates, statins, and diuretics. Despite advances in treatment options, patients with HF continue to have high morbidity and mortality [1]. Often patients are being told that treatment options have been exhausted. The prognosis of patients with HF is very poor, with a median survival of only 1.7 years in men and 3.2 years in women [2]. Since the Framingham Heart Study, the survival rate has improved, yet morbidity and mortality from heart failure continues to remain high. Approximately 50% of patients die within five years of initial diagnosis [1]. It is a paradox that despite the improvement of the management of all forms of IHD, there is an increasing occurrence of HF.

Deprivation of cardiac bioenergy has a major role in HF [3]. The heart consumes more energy than any other organ. This bioenergy is provid-

Table 1. Composition of micronutrient program

Ingredient	Compound	Daily dose
Vitamin A	Natural mixed carotenoids	1,584 IU
Vitamin C	Ascorbic acid, ascorbyl palmitate, calcium ascorbate, magnesium ascorbate	2,450 mg
Vitamin D3	Cholecalciferol	130 IU
Vitamin B1 (Thiamin)	Thiamin mononitrate	22 mg
Vitamin B2 (Riboflavin)	Riboflavin	22 mg
Vitamin B3 (Niacin)	Niacin, niacinamide	75 mg
Vitamin B5 (Pantothenic acid)	Calcium d-pantothenate	80 mg
Vitamin B6 (Pyridoxine)	Pyridoxine HCl	14 mg
Folic acid		90 mcg
Vitamin B12	Cyanocobalamin	27 mcg
Vitamin E	Mixed tocopherol, d-alpha tocopheryl succinate	300 IU
Biotin		195 mcg
Calcium	Calcium glycinate, dicalcium phosphate, calcium ascorbate	322 mg
Phosphorus	Dicalcium phosphate	15 mg
Magnesium	Magnesium ascorbate	510 mg
Zinc	Zinc glycinate	7 mg
Selenium	L-selenomethionine	20 mcg
Copper	Copper glycinate	0.3 mg
Manganese	Amino acid chelate	1.3 mg
Chromium	Chromium glycinate	10 mcg
Molybdenum	Molybdenum glycinate	4 mcg
Potassium	Amino acid chelate	20 mg
L-lysine	L-lysine HCl	1,110 mg
L-proline		110 mg
L-arginine	L-arginine HCl	790 mg
L-cysteine	L-cysteine HCl	35 mg
L-carnitine	L-carnitine tartrate	195 mg
Taurine		200 mg
Bioflavonoid	Citrus fruit peel bioflavonoid complex	410 mg
Inositol		35 mg
Mixed tocopherols	Beta, gamma, delta tocopherols	25 mg
Coenzyme Q10		27 mg
Pycnogenol		7 mg
Mixed carotenoids	Alpha carotene, lutein, zeaxanthin, cryptoxanthin	68.5 mcg

ed by the biochemical conversion of glucose and fatty acids into mechanical energy supporting the heart muscle functions. However, instead of its focus being on a natural increase in the bioenergy supply, the majority of medical approaches focus on energy-sparing effects by using medicines such as, beta-receptor blockers, ACE inhibitors, or angiotensin II blockers. Although these approaches result in improvements of some of the symptoms of HF, they do not address its underlying cause, which is insufficient bioenergy production in the heart myocytes. There is a growing body of evidence suggesting that micronutrients play an important role in the etiology and prognosis of HF [4-7]. Most studies on heart failure in the past using micronutrients have been conducted with a single nutrient or two nutrients. There are suggestions to investigate the effects of multiple nutrients on heart failure [8, 9]. Two studies on heart failure using multiple micronutrients produced dissimilar results [10, 11]. The reason could be the difference in the dosage of the nutrients and the age group of the subjects. However, both of these studies did not use any amino acids. Other than L-carnitine which has positive effects on HF, amino acids such as L-lysine and L-proline are very important because, together with vitamin C, they form part of the collagen molecules which are crucial

Table 2. Baseline characteristics of the study group (n = 12)

Characteristics	All patients No (%)
Age: 35-49	0 (0%)
Age: 50-59	9 (75%)
Age: 60-69	1 (8.3%)
Age: 70 and above	2 (16.7%)
Gender: Male	9 (75%)
Gender: Female	3 (25%)
High blood pressure	7 (58.3%)
Low blood pressure	2 (16.7%)
High blood sugar	4 (2 on insulin) (33.3%)
Angina	7 (58.3%)
Arrhythmia	3 (25%)
Dyspnea	8 (66.7%)
Previous cardiac event	5 (41.7%)
Valvular heart disease	2 (16.&%)
Hypertrophic cardiomyopathy	2 (16.7%)
Currently on medications	12 (100%)
NYHA Class II	6 (50%)
NYHA Class III	4 (33.3%)
NYHA Class IV	2 (16.7%)

to the strengthening of artery walls to prevent atherosclerosis [12, 13].

The aim of this study was to assess the influence that a multiple micronutrient supplementation has on quality of life (QOL) in patients with HF secondary to IHD.

Materials and methods

Subjects

This study is a prospective case series of outcomes from a group of HF patients secondary to IHD patients who were treated with a nutritional supplement program. In addition, case data from the patients were analyzed from a variety of perspectives to look for trends in response to treatment and adverse effects.

All patients described in the case series were informed and they consented for participation. They were followed at the Natural Harmony Therapy Centre, an integrated healthcare center located at Petaling Jaya, Malaysia. Case records were in hand written case notes. The start and end of case records were September 2014 and May 2015, respectively. A follow-up visits with each patient was scheduled monthly, and the mean duration of follow-up was four months. The prime manifestations of the patients in this case series were dyspnea and fatigue, limited exercise tolerance, fluid retention, pulmonary congestion, and edema of the lower extremities. All patients had either a previous myocardial infarction event or were scheduled for heart by-pass surgery.

Inclusion and exclusion criteria

Inclusion criteria for patients with HF were as follows: 1. Age 35 to 75. 2. New York Heart Association (NYHA) class II, III and IV. 3. HF due to IHD. 4. Stable with regard to standard protocol treatment (these patients are usually on ACE inhibitors or diuretics) for the diagnosed condition of at least three months in duration with no exacerbation or change in medication.

Exclusion criteria were as follows: 1. Persistent atrial fibrillation. 2. Patients on anti-inflammatory therapy. 3. Myocarditis. 4. Advanced kidney and liver damage. 5. Malabsorption. 6. Pregnant and lactating women.

Outcome measure

The primary outcome measure utilized the Minnesota Living with Heart Failure Questionnaire (MLHFQ) for therapeutic outcome. The MLHFQ is a validated patient-reported outcome measurement tool used in measuring patient-perceived changes in symptoms, functional limitations, and psychological distress, to be scored on a 0 to 5 Likert scale. The measures were combined to provide symptoms score (fatigue, shortness of breath and swollen ankles), and an overall profile score that allowed for quantifiable assessment of overall change over time. The MLHFQ was used to record severity during the initial case taking and on each scheduled monthly return visit. The compilation of data was undertaken using Microsoft Excel. Simple description statistics and paired T-test were used for analysis of the quantifiable data. A positive change of 5 points in the MLHFQ would have a clinically significant effect [14].

Intervention

Patients were given high-potency-multivitamin/mineral/amino acid supplements in three daily doses, in addition to all prescribed convention-

Table 3. Demographics of patients treated with nutritional supplement program

Patient	Age	Sex	Diagnosed conditions/symptoms	Concurrent medications	Follow-up in Month	NYHA class
1	50	F	HF with pulmonary hypertension, angina, arrhythmia, dyspnea	Sildenafil, digoxin furosemide, spironolactone	8	IV
2	71	M	General lethargy, arrhythmia, dyspnea, hypertension	Statin, furosemide, enalapril	3	II
3	56	M	HF with hypertrophic cardiomyopathy, arrhythmia, angina, dyspnea	Digoxin, atenolol, spironolactone	3	III
4	54	F	Angina, dyspnea, pituitary tumour, hypertension	Digoxin, irbesartan, spironolactone	4	IV
5	50	M	Arrhythmia, angina, tachycardia	Statin, atenolol	4	II
6	54	M	Hypertrophic cardiomyopathy, diabetes, pancreatitis	Insulin, digoxin, enalapril, statin	3	III
7	52	M	Angina, diabetes, hypothyroidism	Metformin, bisoprolol, statin	5	II
8	74	F	Diabetes, hypertension, angina, dyspnea	Insulin, irbesartan, furosemide, statin	4	III
9	63	M	Angina, dyspnea	Statin, bisoprolol	7	II
10	51	M	Myocardial infarct, bradycardia, hypertension, ankylosing spondylosis, dyspnea	Statin, enalapril, spironolactone	5	II
11	56	M	Angina, dyspnea, hypertension	Statin, enalapril, spironolactone	3	III
12	61	M	CAD-severe stenosis, angina, diabetes, hypertension	Statin, atenolol, metformin, furosemide	5	II

Table 4. Change in MLHFQ total score, paired T-test, mean (SD), and *P* value

Patient	Baseline	Endpoint	Change
1	71	3	68
2	66	42	24
3	45	30	15
4	28	16	12
5	21	7	14
6	64	14	50
7	11	3	8
8	70	58	12
9	39	9	30
10	41	10	31
11	11	5	6
12	63	8	55
Total	530	205	325
Mean (SD)	44.17 (22.66)	17.08 (17.36)	27.08 (20.43)
P value			< 0.001

SD-Standard Deviation.

Table 5. Change in MLHFQ symptoms score (fatigue, shortness of breath, and swollen ankles), paired T-test, mean (SD), and *P* value

Patient	Baseline	Endpoint	Change
1	13	1	12
2	10	6	4
3	7	6	1
4	5	2	3
5	3	2	1
6	10	2	8
7	5	0	5
8	16	10	6
9	5	1	4
10	4	2	2
11	2	0	2
12	8	0	8
Total	88	32	56
Mean (SD)	7.33 (4.23)	2.67 (3.08)	4.67 (3.34)
P value			< 0.005

al medications. The list of ingredients of the supplements is in **Table 1**. Compliance with the nutritional supplement program was monitored during monthly follow-up visits.

Results

Baseline characteristics of the study group

The baseline characteristics of the study group, as assessed from the patients' records, are presented in **Table 2**. Of the total number (n = 12), 9 patients were males and 3 were females. The mean age was 57.7 years ± 8.0 years (range 50 to 74 years). The demographics of all the patients are summarized in **Table 3**. The most commonly prescribed medications were statins, ACE inhibitors, angiotensin receptor blockers, beta-blockers, loop diuretics, aldosterone antagonist, and digoxin. Most patients were also prescribed with blood thinners.

Data from MLHFQ

Tables 4 and **5** summarize the MLHFQ data collected, taking into account the baseline and endpoint for all the patients. The patients answered all twenty-one questions in the MLHFQ. The median MLHFQ total score and symptoms score (swollen ankles, shortness of breath, and fatigue) at baseline were 41 and 7.5, respectively, while the mean total score was 44.17 ± 22.66 and symptoms score was 7.33 ± 4.23. At endpoint, the median was 30.5 for total score and 5 for symptoms score, while the mean was 17.08 ± 17.36 for total score and 2.67 ± 3.08 for symptoms score. Mean change was 27.08 ± 20.43 for total score and 4.67 ± 3.34 for symptoms score.

Paired T-test results showed there is a statistically significant (P < 0.001) difference between the baseline and endpoint of treatment.

MLHFQ data in relation to NYHA functional classification

Of the twelve patients in the study group, six were in NYHA class II, four in class III, and two in class IV. **Table 6** summarizes the mean change for total and symptoms score in relation to NYHA functional classification.

Discussion

All the patients in the study group were on appropriate medications for HF. Their conditions at baseline were stable with regards to their diagnosed condition of more than three months duration with no exacerbation or change in medication. From the MLHFQ data, the mean positive change in total score is 27.08. This is far much higher than the 5 points positive change in total score in order to be considered clinically significant as suggested by Rector and colleagues [14]. The results show

Table 6. Mean change in total and symptoms score in relation to NYHA functional classification, paired T-test, mean (SD) and *P* value

NYHA class	Patients	Mean change total score	Mean change symptoms score
II	2, 5, 7, 9, 10, and 12	27	4
III	3, 6, 8 and 11	21	4.25
IV	1 and 4	40	7.5
Total		88	15.75
Mean		29.33 (9.71)	5.25 (1.95)
P value			< 0.013

that it is both statistically ($P < 0.001$) and clinically significant.

The patients in all the three NYHA functional classification groups showed significant improvements with the highest positive change (mean total score at 40 and mean symptoms score at 7.5) recorded in patients in the NYHA class IV. This suggests that patients who had more severe symptoms and overall HF conditions experienced more improvement compared to those who were less severe. However, with only two patients in the NYHA class IV group, it may bias the observation.

This case series study used a fairly high dosage (above the RDAs) of the multiple micronutrients. It also used multiple amino acids such as L-lysine, L-proline, L-arginine, L-carnitine, L-cysteine, and taurine, which are important nutrients for cardiac functions. The earlier studies of Witte and colleagues [10] and McKeag and colleagues [11] did not use any amino acids as part of the micronutrient intervention. Furthermore, the vitamin C dosage used in this study was much higher than those used in the two earlier studies. Vitamin C is important, as it has been shown in a large-scale observational study that the risk of HF decreases with increasing plasma vitamin C [15]. Furthermore, the use of vitamin C, lysine and proline is crucial for the body's production of collagen and the protection of the endothelium of the artery walls [13].

The study of HF endpoints requires precise objective and subjective outcome measures. Although this study used only one outcome measure, the MLHFQ, it nevertheless has succeeded to detect a significant treatment effect. The conclusion from this study suggests that high dose multiple micronutrients may have an important role in the pathophysiology in IHD and HF.

The result of this study corroborates with the findings of Rath and Niedzwiecki [16] whereby a similar nutritional supplement program halted the progression of early coronary artery disease. A recent study on the effect of vitamin C on transgenic mice that mimic human pathophysiology [17] lends credence to the hypothesis of Rath and Pauling that the primary cause of the deposition of lipoprotein(a) [Lp(a)] and atherosclerosis is due to the deficiency of vitamin C [12]. The transgenic mice, when deprived of vitamin C in the diet, developed lesions in the coronary arteries and finally Lp(a) deposition.

The duration of follow-up is rather short, ranging from three to eight months. This is because six patients were lost to follow-up. At the endpoint, six other patients are still on the nutritional supplement treatment protocol.

There were no adverse events recorded during the follow-up treatment. However, from case records, some of the elderly patients in the study group had an initial aggravation of symptoms during the first few days. When the supplements were tapered to a single dose per day for three days, and thereafter slowly increased to three doses a day in the following week, the discomfort symptoms alleviated. This would suggest that due to a rapid boost in cellular bioenergy production the dose of micronutrients should be adjusted gradually. Half of the patients had loose bowel during the initial stage of taking the supplements. This might have been due to the high dose of vitamin C that the patients were not accustomed to taking.

This prospective case series study on HF patients secondary to IHD, using quality of life outcome measure, shows that a high dose of multiple micronutrients has beneficial effects on cardiac function in patients with symptomatic heart failure, and therefore may have an important role in the pathophysiology of IHD and HF. More long-term studies with rigorous study designs to test the efficacy of the micronutrients and their safety are indicated.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Aleksandra Niedzwiecki, Dr. Rath Research Institute, 1260 Memorex Drive, Santa Clara, CA 95050, USA. E-mail: author@drrath.com

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