

Thiamine supplementation in patients with chronic heart failure receiving optimum medical treatment

Abstract

Background: Thiamine deficiency may cause heart failure and symptoms including edema, palpitation, tachycardia, weakness, malaise, and dyspnea due to water and salt retention and peripheral vasodilation. Patients with heart failure might be thiamine deficient and benefit thiamine supplementation. This study was designed to evaluate the effect of thiamine supplementation on some systolic and diastolic echocardiographic parameters and signs and symptoms of heart failure.

Methods: Fifty two patients with systolic heart failure (LVEF < 40%) receiving optimum medical treatment, were randomized to receive 300mg thiamine or placebo for 1 month in a double-blind fashion (26 patients in each group). Echocardiographies were performed before and after treatment by a single investigator and sign and symptoms were evaluated (clinicaltrials.gov Identifier # NCT01115504).

Results: Mean age was 61.44 ± 11.8 years and 67.3% were male. Maximal systolic tissue velocity of septal and lateral walls (Sm waves) increased 0.99 ± 1.46 and 0.83 ± 1.58 cm/s in thiamine group and changed 0.005 ± 1.63 and -0.1 ± 1.83 cm/s in placebo group ($P = 0.033$ and $P = 0.044$) respectively. Ejection fraction or diastolic echocardiographic parameters were not influenced by thiamine supplementation and there was no significant effect on daily activities and dyspnea. However, peripheral edema improved in 9 patients (34.6%) of thiamine group versus 1 of the placebo group (3.8%) ($P = 0.005$).

Conclusion: In the present study thiamine supplementation had some positive effect on edema and systolic function through an increase of lateral and septal Sm. However usefulness of routine supplementation needs more study.

Keywords: thiamine, heart failure, edema, signs and symptoms, echocardiography

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Introduction

Despite the improvement in the treatment of heart failure the mortality still remains high and it causes significant morbidity and costs worldwide.¹ Thiamine (vitamin B1) is one of water soluble vitamins² that could be available in cereal grains, nuts, yeast and meat.³ Thiamine has an important role in cellular process and its deficiency may cause retention of sodium and water and development of vasodilation.³ Thiamine deficiency has been related to a known high cardiac output heart failure,¹ traditionally known as Beriberi with manifestations including edema, palpitation, tachycardia, weakness, malaise, dyspnea, pain or paresthesia of lower extremity and decreased diastolic blood pressure with a wide pulse pressure.³

There are some evidences that heart failure patients might be thiamine deficient in comparison to healthy controls;⁴⁻¹⁰ Heart failure patients tend to have inadequate nutrient intake,³⁻⁵ on the other hand, loop^{4,5,11-16} and all other diuretics^{11,15} that may be used in heart failure may cause the hyperexcretion of thiamine,^{2,4,5,13-15,17} hence chronic diuretic treatment has been related to thiamine deficiency in a high risk patient (such as an elderly) in some^{2,6,11,13,17,18} but not all of the studies.^{7,19,20} Thiamine deficiency further impairs cardiac performance in heart failure,¹³ and can mimic its signs and symptoms.⁵ It is possible that thiamine supplementation has some useful effects in the patients with heart failure^{2,3,17} by prevention or correction of thiamine deficiency in heart failure,^{4,13,14} but this is controversial.^{2,4,7,17,21}

Considering the low cost and minimal side-effects of thiamine-replacement therapy, and lack of randomized clinical trials regarding the favorable effect of thiamine, this prospective randomized double blind study was performed to consider the effect of thiamine

supplementation on systolic and diastolic heart function and symptoms and signs of patients with heart failure.

Materials/patients and methods

Between May 2010 and Jan 2011, 52 systolic heart failure patients (LVEF $\leq 40\%$, NYHA class II) who were routinely visited in a heart clinic (in Shahrud, Iran) and were on optimal tolerated medical therapy, were enrolled in the study. The inclusion criteria were absence of any change in clinical signs and symptoms or drug regimen of the patients in the past 3 months, due to aggravated symptoms or optimization of dosage for a survival benefit according to the present guidelines. Excluded patients were those with decompensated heart failure, bradycardia or tachycardia (needing a change in drug dosage or regimen), concomitant medical illness e.g. chronic renal failure, chronic obstructive pulmonary disease, asthma and uncontrolled hypertension.

The study was a single-site randomized placebo-controlled double blind trial and enrolled patients were randomized by means of block randomization method by a single pharmacist. Patients were assigned to randomly receive 300mg daily of thiamine (HakimVitamin B1300®, Hakim pharmaceutical industry, Tehran, Iran) (n=26, thiamine group) or placebo (Hakim pharmaceutical industry, Tehran, Iran) (n=26, placebo group) for 30 days in a double-blind fashion.

At randomization and at the end of study, echocardiography (Sonace 8000 EX, South Korea) was performed by a single operator in a blinded fashion. Ejection fraction was measured in 2D echocardiography in apical 4 chamber and apical 2 chamber views by means of Simpson method. systolic velocity of myocardial tissue of septal and lateral walls (Sm waves) were obtained by tissue

Doppler imaging of lateral and septal wall of the left ventricle, using pulsed Doppler echocardiography with the 2 to 3mm sample volume positioned about 1cm from the mitral annulus in apical 4-chamber view. Early diastolic filling velocity of the left ventricle (E wave) was obtained using pulsed Doppler echocardiography with the 2 to 3mm sample volume positioned at the mitral leaflet tips with the beam aligned parallel to stream in apical 4-chamber view.²² Early diastolic myocardial tissue velocity (Ea wave) was obtained using pulsed Doppler echocardiography with the 2 to 3mm sample volume positioned in the myocardium of the basal ventricular wall, about 1cm from the mitral annulus from the basal septum and basal lateral walls in apical 4-chamber view.²² E wave and septal and lateral Ea waves were recorded at end expiration during normal breathing.²² Septal E/Ea and lateral E/Ea were calculated as markers of diastolic function.

Weight was measured in Kg and body mass index was presented in Kg/m². Assessment of symptoms was done by means of a self scoring system (from 1 to 7) with an inter-observer error of <5% and quality of life was assessed LAMY-7 questionnaire. Patients gave scores to "Vigorous exercise", "Light exercise", "Usual daily activities", "Dyspnea", "Chest pain", "musculoskeletal pain", "Anxiety" and "General well-being" at randomization and again after 30days of treatment. Score 1 was given if the patient felt the symptoms were terrible, score 2 if very bad, score 3 if bad, score 4 if moderate, score 5 if good, score 6 if very good and score 7 if he or she felt excellent. So the more the score the better was the situation. At the second review after 30days of therapy with thiamine or placebo the patients were asked to score to the same questionnaire and increase the scores if they believed to be better or decrease the scores if they felt worse. "Edema was objectively scored 1 to 7 at randomization and after 30 of treatment by a single experienced. Local ethical committee approved the study and informed consents were obtained.

The primary outcome of the study was an increase in dyspnea score. The secondary end points were improvement in edema or systolic function of the heart as measured by ejection fraction, lateral and septal Sm wave (measured by tissue Doppler).

Statistical analysis

Sample size calculations were based a pilot study assuming 20% improvement in dyspnea in thiamine group and 10% improvement in placebo group. In order to detect a 10% difference in the dyspnea change between active and placebo with 80% power, at a 5% two-tailed significance 21 patients per group were to be enrolled in this study.

SPSS 16 was used for data analysis. Numerical variables were presented as mean \pm standard deviation and categorical variables were summarized by raw numbers and percentages. Quantitative data were compared by means of student T test if they showed a normal distribution and non-parametric tests if not. Qualitative data were tested by means of Chi square tests and Fisher exact test if appropriate and odds ratios are presented. Multivariate analysis was performed by linear regression (backward method) or binary logistic regression tests by backward Wald methods if appropriate. Age, sex and those variables with p value of less than 0.1 in univariate analysis were included in the model. P values of less than 0.05 were accepted significant.

Results

Mean age of the study group was 61.44 ± 11.8 years and 67.3% were male. Mean ejection fraction was 32.98 ± 5.51 percent at randomization. Ten patients (19.2%) were treated with furosemide and

the prevalence of prescription of hydrochlorothiazide, spironolactone, angiotensin converting enzyme inhibitors (ACE Inhs), angiotensin receptor blockers (ARBs), beta-adrenergic blockers and digoxin were: 7 (13.5%), 46 (88.5%), 10 (19.2%), 42 (80.8%), 44 (84.6%), 33 (63.5%) respectively. A comparison of baseline characteristics in thiamine and placebo group is shown in Table 1.

1. Scores were given to each variable from 1 to 7.
2. Septal Sm wave: Maximal systolic velocity of myocardial tissue in tissue Doppler imaging of septal wall of the left ventricle.
3. Lateral Sm wave: Maximal systolic velocity of myocardial tissue in tissue Doppler imaging of lateral wall of the left ventricle.
4. Mitral E wave: Peak mitral inflow velocity of the early rapid filling wave.
5. Septal Ea wave: Early diastolic myocardial tissue velocity of septal wall of the left ventricle.
6. Lateral Ea wave: Early diastolic myocardial tissue velocity of lateral wall of the left ventricle.

Improvement of signs and symptoms and echocardiographic determinants of systolic and diastolic cardiac function are summarized in Table 2. Dyspnea improved in 6 patient (23.1%) of thiamine group in comparison to 3 (11.5%) of placebo group (P=0.46). Nine patients of thiamine group (34.6%) versus 1 of the placebo group (3.8%) reported improvement of edema (P = 0.005, odds ratio=13.24, 95% confidence interval = 1.53 – 114.29). Multivariate analysis showed among included variables (age, sex, spironolactone and thiamine intake) thiamine had a significant independent role in improvement of edema (Ex B = 13.24, 95% confidence interval = 1.53 – 114.29, P = 0.019).

1. Septal Sm wave: Maximal systolic velocity of myocardial tissue in tissue Doppler imaging of septal wall of the left ventricle.
2. Lateral Sm wave: Maximal systolic velocity of myocardial tissue in tissue Doppler imaging of lateral wall of the left ventricle
3. Mitral E wave: Peak mitral inflow velocity of the early rapid filling wave.
4. Septal Ea wave: Early diastolic myocardial tissue velocity of septal wall of the left ventricle.
5. Lateral Ea wave: Early diastolic myocardial tissue velocity of lateral wall of the left ventricle.

Table 3 summarizes changes in different quantitative variables after 30days of thiamine or placebo administration. Thiamine did not improve any of other symptoms including, vigorous and light exercise score, usual daily activities, chest pain, musculoskeletal pain, anxiety and general well-being (Table 3). Septal and lateral Sm waves increased 0.99 ± 1.46 and 0.83 ± 1.58 cm/s in thiamine group and changed 0.05 ± 1.63 and -0.1 ± 1.83 cm/s in placebo group respectively (P = 0.033 and P = 0.044, Table 3). In multi-variate analysis among possible variables that presumed to have an influence on septal and lateral Sm, there was a trend of increase in septal and lateral Sm in thiamine group ($\beta = -0.22$, P = 0.082 and $\beta = -0.24$, P = 0.072 respectively).

1. Scores were given to each variable from 1 to 7.
2. Septal Sm wave: Maximal systolic velocity of myocardial tissue in tissue Doppler imaging of septal wall of the left ventricle.

3. Lateral Sm wave: Maximal systolic velocity of myocardial tissue in tissue Doppler imaging of lateral wall of the left ventricle.
4. Mitral E wave: Peak mitral inflow velocity of the early rapid filling wave.
5. Septal Ea wave: Early diastolic myocardial tissue velocity of septal wall of the left ventricle.
6. Lateral Ea wave: Early diastolic myocardial tissue velocity of lateral wall of the left ventricle.

Considering any increases of septal and lateral Sm waves as independent variables, 19 patients of thiamine group (73.1%) versus 12 of the placebo group (46.2%) showed an increase in septal and lateral Sm waves (The results were the same for both, $P=0.048$, odds ratio = 3.17, 95% confidence interval = 0.99 – 10.1, table 2).

Table 1 Baseline characteristics of the thiamine and placebo groups. Qualitative data are shown as number (%) and quantitative data are shown as mean \pm standard deviation

Variable	Thiamine Group	Placebo Group	P value
Male	16 (61.5%)	19 (73.1%)	0.38
History of myocardial infarction	16 (66.7%)	16 (76.2%)	0.48
Furosemide	6 (23.1%)	4 (15.4%)	0.73
Hydrochlorothiazide	3 (11.5%)	4 (15.4%)	1
Spirolactone	22 (84.6%)	24 (92.3%)	0.67
Angiotensin converting enzyme inhibitors	4 (15.4%)	6 (23.1%)	0.48
Angiotensin receptor blockers	22 (84.6%)	20 (76.9%)	0.48
Beta-adrenergic blockers	21 (80.8%)	23 (88.5%)	0.44
Digoxin	17 (65.4%)	16 (61.5%)	0.77
Age (years)	61.92 \pm 10.73	60.96 \pm 12.94	0.77
Weight (Kg)	66.62 \pm 12.19	70.87 \pm 13.87	0.25
Body mass index (Kg/m ²)	25.54 \pm 4.1	26.04 \pm 4.61	0.68
Dyspnea score	5.96 \pm 1.25	5.85 \pm 1.35	0.76
Vigorous exercise score	2.27 \pm 1.89	2.54 \pm 2.16	0.69
Light exercise score	5.08 \pm 1.52	5.08 \pm 1.81	1
Usual daily activities score	6.8 \pm 0.98	6.73 \pm 0.83	0.33
Chest pain score	6.12 \pm 1.34	6.31 \pm 1.16	0.67
Musculoskeletal pain score	6.08 \pm 1.35	6.38 \pm 0.75	0.76
Anxiety score	5.46 \pm 1.68	5.23 \pm 1.66	0.63
General well-being score	5.5 \pm 1.03	5.35 \pm 0.8	0.61
Edema score	5.54 \pm 1.48	5.96 \pm 1.22	0.36
Dyspnea score	5.96 \pm 1.25	5.85 \pm 1.35	0.76
Vigorous exercise score	2.27 \pm 1.89	2.54 \pm 2.16	0.69
Light exercise score	5.08 \pm 1.52	5.08 \pm 1.81	1
Usual daily activities score	6.8 \pm 0.98	6.73 \pm 0.83	0.33
Chest pain score	6.12 \pm 1.34	6.31 \pm 1.16	0.67
Musculoskeletal pain score	6.08 \pm 1.35	6.38 \pm 0.75	0.76
Ejection fraction (percent)	32.79 \pm 5.26	33.17 \pm 5.85	0.81
Septal Sm wave (cm/s)	6.45 \pm 1.75	6.36 \pm 1.28	0.84
Lateral Sm wave (cm/s)	6.43 \pm 1.94	7.01 \pm 1.84	0.27
Mitral E wave/ Septal Ea wave	14.94 \pm 10.49	13.31 \pm 7.7	0.55
Mitral E wave/ lateral Ea wave	13.5 \pm 10.62	12.05 \pm 4.6	0.63
Systolic blood pressure (mm Hg)	125.4 \pm 15.6	124.5 \pm 19.9	0.89
Diastolic blood pressure (mm Hg)	73.8 \pm 9.4	70.9 \pm 9	0.2
Heart rate (beat/min)	68.3 \pm 10.9	71.1 \pm 10.3	0.34

Table 2 Changes in different qualitative variables after 30 days of therapy with thiamine or placebo. Data are presented as number (%)

Variable	Thiamine Group	Placebo Group	P value
Any increase in weight	10 (41.7)	11 (45.8)	0.77
Any improvement in dyspnea	6 (23.1)	3 (11.5)	0.47
Any improvement in vigorous exercise	1 (3.8)	4 (15.4)	0.35
Any improvement in light exercise	8 (30.8)	6 (23.1)	0.53
Any improvement in usual daily activities	0	0	0.999
Any improvement in chest pain	8 (30.8)	4 (15.4)	0.19
Any improvement in musculoskeletal pain	3 (11.5)	3 (11.5)	0.999
Any improvement in anxiety	10 (38.5)	6 (23.1)	0.23
Any improvement in general well-being	6 (23.1)	3 (11.5)	0.47
Any improvement in edema	9 (34.6)	1 (3.8)	0.005
Any increase in ejection fraction	5 (19.2)	7 (26.9)	0.51
Any increase in septal Sm wave (cm/s)	19 (73.1)	12 (46.2)	0.05

Table Continued...

Variable	Thiamine Group	Placebo Group	P value
Any increase in lateral Sm wave (cm/s)	19 (73.1)	12 (46.2)	0.05
Any decrease in mitral E wave/ Septal Ea wave	9 (34.6)	15 (57.7)	0.1
Any decrease in mitral E wave/ lateral Ea wave	12 (46.2)	14 (53.8)	0.58

Table 3 Changes in different quantitative variables after 30 days of therapy with thiamine or placebo

Variable	Thiamine Group (Mean ± SD)	Placebo Group (Mean ± SD)	P value
Weight (Kg)	0.9 ± 2.22	1.44 ± 5.86	0.69
Dyspnea score	0.27 ± 0.67	-0.04 ± 0.82	0.052
Vigorous exercise score	-0.19 ± 0.57	-0.04 ± 0.82	0.11
Light exercise score	0.35 ± 1.5	0.12 ± 1.45	0.83
Usual daily activities score	0 ± 0	-0.04 ± 0.2	0.32
Chest pain score	0.46 ± 1.07	0.23 ± 1.18	0.25
Musculoskeletal pain score	-0.27 ± 1.15	-0.19 ± 1.17	0.5
Anxiety score	0.62 ± 1.36	0.35 ± 1.44	0.54
General well-being score	0.19 ± 0.75	-0.08 ± 0.74	0.22
Edema score	0.58 ± 1.17	-0.15 ± 0.67	0.008
Systolic blood pressure (mm Hg)	-6.92 ± 14.9	-5.69 ± 17.64	0.54
Diastolic blood pressure (mm Hg)	-6.15 ± 10.23	-2.88 ± 7.26	0.25
Heart rate (beat/min)	1.5 ± 10.82	2.58 ± 10.48	0.72
Ejection fraction (percent)	0.87 ± 2.44	0.00 ± 3.46	0.64
Septal Sm wave (cm/s)	0.99 ± 1.46	0.05 ± 1.63	0.033
Lateral Sm wave (cm/s)	0.83 ± 1.58	-0.1 ± 1.83	0.044
Mitral E wave/ Septal Ea wave	-1.76 ± 7.15	-1.35 ± 4.48	0.82
Mitral E wave/ lateral Ea wave	-1.58 ± 6.53	-1.08 ± 4.68	0.77

Discussion

The effect of thiamine supplementation left ventricular function is not clear in patients with heart failure.¹⁷ Seligmann and colleagues and reported that oral thiamine supplementation increased left ventricular ejection fraction in 5 heart failure patients with thiamine deficiency.¹³ Shimon and associates as well as Schoenenberger and coworkers reported similar results in heart failure patients with long-term diuretic therapy.^{23,24} Witte et al. prescribed capsules containing a combination of high-dose micronutrients including thiamine to 30 heart failure patients for 9 months and reported a reduction in LV volumes and an increase in LVEF.²⁵

In our study maximal systolic velocity of myocardial tissue of septal and lateral walls (septal and lateral Sm waves) increased in thiamine group (P = 0.033 and P = 0.044, Table 3). This velocity is an indicator of ventricular systolic function^{26,27} and correlates well with LVEF.²⁷ However we could not show a significant increase in LVEF by thiamine supplementation in contrast to placebo (0.87 ± 2.44 percent increase in LVEF in thiamine group and no increase in placebo group P = 0.64, Table 3), which might be due to our limited sample size. On the other hand only 19.2% of our patients were treated with furosemide (≤80mg/d) and prevalence of prescription of hydrochlorothiazide and spironolactone, were 13.5% and 88.5% respectively. Considering that spironolactone might increase thiamine level in heart failure patients on loop diuretics²⁸ we postulated that our study group might have higher blood thiamine, that might have an effect on the possible beneficial effects of thiamine supplementation on some signs and symptoms as well as ejection fraction.

To evaluate the possible effect of thiamine supplementation, using septal and lateral E/Ea waves we could not show any significant improvement in diastolic function. E/Ea ratio which is a combination of peak mitral inflow velocity of the early rapid filling wave (E wave) and early diastolic myocardial tissue velocity (Ea wave) may have a good relationship to left ventricular filling pressure.²⁶⁻³⁰ The results of our study showed that scores of dyspnea trended to improve by

thiamine supplementation. Seligmann et al noticed that symptoms related to functional capacity improved by at least one New York Heart Association class in all 6 of their studied patients treated with a 7-day course of 100 mg twice daily intravenous thiamine.¹³ Dyspnea as one of the most important symptoms of heart failure seems to be correlated not only to systolic dysfunction but also to end diastolic pressure. We postulated that absence of significant improvement in scores to dyspnea or symptoms like vigorous exercise, light physical activities and usual daily activities (Table 2) in spite of significant increase in lateral and septal Sm in our study group could be due to the absence of significant effect of thiamine on E/Ea wave and hence diastolic function.

Our patients reported an improvement in edema with thiamine supplementation (9 patients (%34.6) of thiamine group versus 1 (%3.8) of placebo group (P = 0.005, Table 2), that was confirmed with multivariate analysis. This novel finding in the present study suggests that thiamine supplementation could have a positive effect on edema. It has been shown that in older heart failure patients on diuretic treatment, low dose thiamine supplementation may help to prevent the development of a sub clinical wet-beriberi¹⁶ and possibly edema. Thus thiamine could be considered as a complementary drug in the treatment of heart failure patients with edema. Weakness and malaise could occur in thiamine deficiency.³ In our study thiamine did not affect scores of general well-being. Witte and his colleagues showed a significant improvement in quality of life by prescription of micronutrients to 30 heart failure patients for 9 months,²⁵ but their regimen contained various types of micronutrients rather than thiamine alone.

Thiamine deficiency may lead to confusion and psychotic symptoms, in addition to neurological signs.³¹ Some physicians prescribe thiamine without clear indication to patients with anxiety symptoms. In the present study thiamine supplementation did not affect scores to anxiety and we do not recommend thiamine prescription for this purpose unless the patient is clearly thiamine deficient. Thiamine deficiency may cause sodium and water retention and peripheral

vasodilation, palpitation, tachycardia and decrease in diastolic pressure due to a widened pulse pressure.³ Seligmann¹³ reported an average increase of 10mm Hg in systolic and diastolic blood pressure in their thiamine deficient patients by 7days of intravenous thiamine administration.¹³ Shimon and associates did not report any significant change in blood pressure in thiamine group.²³ In our study there was no significant change in blood pressure or heart rate of heart failure patients treated with thiamine (Table 3).

Limitations

Measuring thiamine levels in our patients we might lead to better understanding of some of our findings. Including more patients might let us have more powered findings. Given the physiologic importance of thiamine, further investigations aimed at determining the effect in heart failure as well as the safety and efficacy is recommended.

Conclusion

In our study thiamine supplementation had no significant effect on vigorous exercise, light exercise, usual daily activities, dyspnea, chest pain, musculoskeletal pain, anxiety and general well-being, however, it improved edema and Sm wave in echocardiography. We conclude that supplementation of thiamine might be beneficial in patients who suffer from edema, however, further studies are needed to confirm this.

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Conflicts of interest

Author declares there are no conflicts of interest.

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