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THIAMINE SUPPLEMENT THERAPY IMPROVES EJECTION FRACTION VALUE IN STAGE II HEART FAILURE PATIENTS

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ABSTRAK

Tiamin, disebut juga vitamin B1, merupakan vitamin larut dalam air yang terlibat dalam pembentukan ATP dalam sel. Metabolit aktif dari tiamin adalah co-enzim tiamin pyrophosphate (TPP) yang berperan aktif dalam metabolism karbohidrat dan pembentukan konjugasi ikatan asam amino. Secara langsung, tiamin dapat meningkatkan produksi energi dalam sel otot jantung melalui mekanisme tersebut, sedangkan pada kondisi gagal jantung didapatkan penurunan kontraktilitas otot jantung. Oleh karena itu, supplementasi tiamin dibutuhkan pada pasien gagal jantung stage II akibat penggunaan furosemid jangka panjang yang memicu kondisi defisiensi tiamin. Supplementasi tiamin disini difungsikan untuk meningkatkan kontraktilitas sel jantung yang pada akhirnya dapat meningkatkan nilai ejeksi fraksi otot jantung sebagai parameter pengukur efisiensi kerja jantung. Tujuan penelitian ini adalah untuk mengevaluasi pengaruh pemberian tiamin sebagai suplemen terapi pada pasien gagal jantung stage II terhadap perubahan nilai ejeksi fraksi pada pre dan post terapi suplemen tiamin selama 28 hari. Penelitian dilakukan menggunakan metode Observasional Analisis Cross Sectional Prospektif antara bulan April – Agustus 2016 pada pasien gagal jantung pria NYHA II yang mendapat terapi furosemid yang memenuhi kriteria inklusi di Poli Jantung RSI Jemursari, Surabaya. Pasien yang memenuhi kriteria inklusi dan eksklusi pada penelitian ini sebanyak 32 pasien, 16 pasien kelompok kontrol dan 16 pasien kelompok perlakuan dengan usia antara 35-75 tahun. Selama penelitian ini, setelah pemberian suplemen tiamin 300 mg/hari, 16 pasien pada kelompok perlakuan mengalami peningkatan nilai ejeksi fraksi (13,5%). Hasil uji paired t test p=0,000 (p<α; α=0,05) menunjukkan perbedaan bermakna antara nilai ejeksi fraksi pre dan post suplementasi tiamin. Penelitian ini menyimpulkan bahwa pada penelitian didapatkan bahwa terapi suplemen tiamin 300 mg/ hari mampu meningkatkan nilai ejeksi fraksi pada pasien gagal jantung stage II. ***(FMI 2017;53:139-143)***

Kata Kunci*: Defisiensi tiamin, supplementasi, diuretic, ejeksi fraksi*

ABSTRACT

Thiamine, also called vitamin B1, is a water soluble vitamin that is involved in the formation of ATP in cells. The active metabolite of thiamine is a co-enzyme thiamine pyrophosphate (TPP) that plays an active role in carbohydrate metabolism and the formation of amino acid binding conjugates. Directly, thiamine may increase energy production in heart muscle cells through such mechanism, whereas in conditions of heart failure, a decrease in the contractility of heart muscle may be found. Therefore, thiamine supplementation is needed in stage II heart failure patients due to long-term use of furosemide that triggers the thiamine deficiency condition. Thiamine supplementation here is enabled to increase heart cells contractility which may ultimately increase the ejection fraction value of the heart muscle as a parameter of heart work efficiency measurement. The objective of this study was to evaluate the effect of thiamine administration as a therapeutic supplement in stage II of heart failure patients on the ejection fraction rate changes in pre and post thiamine supplement therapy for 28 days. The study was conducted using Cross Sectional Prospective Observational Analysis method between April and August 2016 in male patients with NYHA II heart failure who received furosemide therapy meeting the inclusion criteria at Heart Clinic Jemursari Islamic Hospital, Surabaya. Patients who fulfilled the inclusion and exclusion criteria in this study were 32 patients, 16 control patients and 16 treatment group patients between the ages of 35-75 years. During this study, after supplementation of thiamine 300 mg/day, 16 patients in the treatment group experienced an increase in ejection fraction rate (13.5%). The result of paired t test p=0.000 (p<α; α=0,05) showed significant difference between ejection fraction rate of pre and post thiamin supplementation. This study concluded that thiamine supplement therapy of 300 mg/day could increase the ejection fraction rate in patients of stage II heart failure. ***(FMI 2017;53:139-143)***

Keywords*: thiamine deficiency; supplementation; diuretics; ejection fraction*

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INTRODUCTION

Heart failure is a pathophysiological condition when the heart cannot pump blood at normal speed or simply pump from high filling pressure. Heart failure is defined as clinical syndrome occurring in patients resulting from structural abnormalities and/or heart function resulting in clinical symptoms (dyspnea and fatigue) and signs (edema and rales) that may lead to hospitalization, poor quality of life, and short life expectancy (Brunton et al

2011, Longo et al 2012). Meanwhile, according to the Ministry of Health, heart failure is the inability of the heart to pump enough blood throughout the body, characterized by shortness of breath during moving and/or sleeping on the back without a pillow, and/or swollen lower leg. A patient is said to have a heart failure if he/she has ever been diagnosed with heart failure (decompensatio cordis) by a physician or has not been diagnosed with heart failure but having symptoms/history as mentioned above (Ministry of Health, 2013). Conventional treatment of congestive heart failure, such as loop diuretic administration, may lead to vitamin B1 deficiency (thiamine). Therefore, additional supplements are needed to overcome the side effects of conventional therapies, such as the use of L-Carnitine, Thiamine, Magnesium, D-ribose, fish oil, and others (Larsen 2009).

Thiamine, also called vitamin B1, is a water-soluble vitamin, used in protein, carbohydrate and fat metabolism. In addition, vitamin B1 is also involved in the ATP formation in cells. The active thiamine metabolite is the co-enzyme thiamine pyrophosphate (TPP), playing an active role in the carbohydrate metabolism and the formation of amino acid binding conjugates.

The TPP binds to magnesium (Mg^{2+}) and participates in two types of metabolic reactions: (a) the formation of α-ketols (mostly in the form of hexa and penta phosphate), which is the catalyst for transketolase reaction; (b) the acid-oxidation process of α-keto (e.g. pyruvate, α-ketoglutarate and the acid-conjugated bonds of α-keto) through the dehydrogenase complex formation. In other words, thiamine deficiency will cause a decrease in overall carbohydrate metabolism with all clinical manifestations associated with amino acid metabolism (especially through the α-keto acid pathway) (WHO Expert Consultation 2002). In this case, for example, depression of myocardial muscle function exacerbates the condition of congestive heart failure.

Thiamine supplement is a complementary therapy that works to improve the efficiency of heart muscle work in pumping and minimizing the adverse effects of conventional therapy. The prevalence rate of thiamine deficiency in patients with heart failure is 21-98%. Long-term effects of thiamine deficiency is a deterioration in heart function that can be determined from the value of Left Ventricular Ejection Fraction (LVEF). Another study found that hospitalized patients with a diagnosis of heart failure had thiamine deficiency with a prevalence rate of 55-98% (Larsen 2009).

The clinical conditions of thiamine deficiency are anorexia, weight loss, apathy, short-term memory loss, confusion and fatigue, and muscle weakness. Basically, the clinical condition due to thiamine deficiency is divided into two types, the neuritic type and heart type. In the cardiovascular system, thiamine deficiency results in conditions of palpitation, weakness, and shortness of breath. In severe conditions, the heart muscle enlarges to the right, dizziness, and decreases blood pressure. In fact, heart muscle changes and fluid accumulation in heart muscle fibers may also be seen (WHO Expert Consultation 2002).

MATERIALS AND METHODS

The research was conducted using Cross Sectional Prospective Observational Analysis method. The number of samples involved were 32 patients divided into 16 control patients and 16 patients in the treatment group. The study was conducted in Heart Clinic, Jemursari Islamic Hospital, Surabaya. Sampling was conducted from April to August 2016. Samples taken were those that met the inclusion criteria, while those that did not meet were excluded. After the patient signed the informed consent, monitoring was performed during the therapy period and echocardiography examinations were performed on the research samples at Jemursari Islamic Hospital, Surabaya.

RESULTS

Table 1 shows the demographic data patients sampled, including sex, age, diagnosis, potassium levels after therapy and the type of combined therapy provided. Determination of ejection fraction rate as baseline (hereafter called EF pre) and 28 days after supplementation of thiamine 300 mg/day (hereafter called EF post) for treatment group and control group in the samples was observed using 2 echocardiography observation techniques, ie BiPlane method and Teich method which is determined by ultrasound device of GE® type LOGIC 3. The percentage of ejection fraction rate change of pre- and post-300mg/day thiamine supplementation for control group can be seen in Table 2 and for treatment group can be seen in Table 3.

Table 4 shows the results of ejection fraction comparative test before and after therapy. The results of normality test using Kolmogorov Smirnov showed that baseline fraction ejection data had normal distribution. The p value of 0.021 ($p < \alpha$; $\alpha=0.05$) showed a significant difference in the ejection fraction rates between pre and post supplementations.

Table 1. Patients' demographic data included in inclusion criteria

Distribution	Total		Percentage (%)
	Control Group	Treatment Control	
Age (years):			
35 – 44	2	1	9
45 – 54	5	4	28
55 – 65	9	11	63
Etiology :			
HHD + DCFC II	9	6	47
PJK + DCFC II	4	3	22
PJK +HHD + DCFC II	3	3	19
PJK + DCFC II + Inferior STEMI		1	3
PJK + DCFC II + Inferior OMI		1	3
DCFC II + IMA Anteroseptal		1	3
PJK + DCFC II + AF + HHD		1	3

Table 2. Profile of ejection fraction rate change in control group

Samples	Pre Ejection Fraction (%)	Post Ejection Fraction (%)	Δ BiPlane Ejection Fraction (%)	% Ejection Fraction Changes
1	56.68	67.9	11.22	19.80
2	62.38	60.6	(1.78)	(2.85)
3	55.13	63	7.87	14.28
4	66.14	68.77	2.63	3.98
5	63.03	63.03	0	0
6	57.32	57.05	(0.27)	(0.47)
7	69.62	69.61	(0.01)	(0.01)
8	57.62	57.19	(0.43)	(0.75)
9	48.12	52.91	4.79	9.95
10	58.16	56.31	(1.85)	(3.18)
11	87.76	79.87	(7.89)	(8.99)
12	53.65	55.09	1.44	2.64
13	45.12	37.79	(7.33)	(16.25)
14	47.72	46.17	(1.55)	(3.24)
15	65.12	68.14	3.02	4.64
16	49.16	52.46	3.3	6.72

DISCUSSION

The aim of this study was to evaluate the effect of thiamine administration as a therapeutic supplement in the outpatients of Jemursari Islamic Hospital with stage II heart failure on ejection fraction rate in pre and post 28 days of thiamine supplement therapy with standard furosemide therapy. From the results of the research conducted at the Heart Clinic, Jemursari Islamic Hospital Surabaya in the period of April 5 to August 5 2016, there were 32 male patients with stage II heart failure diagnosis that met the inclusion criteria of the study. The data were collected prospectively and analyzed descriptively.

Table 3. Profile of ejection fraction rate change in treatment group

Samples	Pre Ejection Fraction (%)	Post Ejection Fraction (%)	Δ BiPlane Ejection Fraction (%)	% Ejection Fraction Changes
1	52.42	68.33	30.35	
2	59.61	64.28	7.83	16.27
3	59.07	66.05	11.82	17.36
4	41.37	47.04	13.71	9.46
5	59.04	62.26	5.45	7.83
6	35.82	39.56	10.44	12.00
7	53.12	-	-	16.23
8	38.52	40.71	5.69	1.51
9	51.2	57.74	12.77	4.85
10	40.23	-	-	29.52
11	45.13	52.64	16.64	(20.20)
12	47.14	56.76	20.41	9.25
13	52.21	65.17	24.82	2.33
14	62.38	60.6	(2.85)	11.25
15	66.15	69.17	4.57	5.92
16	58.81	60.17	2.31	10.60

Table 4. Significance profile of the comparative test

No.	Analysis Variables	P Value	Notes
1.	Pre treatment vs pre control	BiPlane 0.000	Significant
2.	Post treatment vs post control	BiPlane 0.021	Significant
3.	Pre treatment vs post treatment	BiPlane 0.000	Significant
4.	Pre control vs pre control	BiPlane 0.509	Not Significant

This study applied primary and secondary data design, but still had many limitations in the use of variables. Not all variables in the theoretical framework could be obtained optimally because there were various obstacles in the field. Several obstacles encountered were the echocardiography examination result of the patients' ejection fraction rate baseline data which did not fulfill the category of stage II heart failure, the minimum number of male patients during the observation period, and the minimum assessment of the patients' clinical condition.

This study was conducted prospectively in patients with stage II heart failure who received furosemide therapy in Heart Clinic of Jemursari Islamic Hospital Surabaya. This study had been conducted for 4 months from April 10 until August 5, 2016. During the study, there were 32 patients who fulfilled the inclusion criteria which were divided into 2 groups, 16 treatment group patients and 16 patients in the control group. From these 32 patients, the patients' demographic data, diagnosis, and therapy obtained by opinion were found.

Demographic data indicated that all patients were male with age range of 35-65 years old. In this study, all samples were male patients and the females were excluded since in females who have menstruation, increased erythrocyte loss may lead to decreased transcetolase enzyme activity. Transcetolase enzyme plays an important role in the formation of thiamine active molecules, i.e. thiamine diphosphate and thiamine pyrophosphate, in which the active thiamin molecular deficiency condition in mitochondrial myocytes may decrease the binding with Mg^{2+} ion. This condition may trigger myocyte cell apoptosis which will ultimately lead to a decrease in energy production from myocytes and furthermore will decrease myocytes contractility. Thus, it can be concluded that if female samples had been included in the population, the research variability and research confounding factors would have increased related to the condition of thiamine deficiency status in the body which required a thiamine dose higher than 300 mg/day.

Diuretic therapy is used in all circumstances that require an increase in water output, and the diuretics frequently used are loop and thiazide. The loop diuretic (furosemide) action mechanism is by blocking the electrolyte (Na/K/Cl2-) in ascending Henle loop. The loop diuretic binds strongly with electrolyte serum that requires secretion in the proximal tubule to be activated, while the electrolyte serum pump (Na/K/Cl2-) is on the luminal side of the nephron. Therefore, the loop diuretic should be able to reach the tubular fluid to become active. The use of long-term diuretics, age factors, dietary factors, and the emergence of some comorbid conditions are risk factors for patients with heart failure to thiamine deficiency. In addition, patients with heart failure have a high basal metabolic that triggers a thiamine deficiency condition. Increased venous pressure in CHF conditions triggers lymphatic product-ion, resulting in compensated lymphatic obstruc-tion in absorption in small intestine that accelerates the thiamine deficiency condition.

Thiamine has many effects on the cardiovascular system. Thiamine has an important hemodynamic effect in blood circulation system as well as the pharmacological positive effects on heart that is increasing the energy production of heart muscle. Several studies have shown that thiamine deficiency causes heart muscle hypertrophy, depression of heart muscle contractility, and dysrhythmias. Clinical trials in patients with CHF showed that thiamine supplementation may increase systolic pressure, diastolic pressure and central venous pressure followed with blood pressure decline and increased LVEF. Thiamine acts as a vasodilator and decreases heart afterload that may improve heart function. Thiamine is also reported to have a positive effect in improving natriuresis of patients with heart failure.

Under normal circumstance, the body stores 25-30 mg of thiamine mostly in skeletal muscle, such as heart, brain, liver, and kidney muscles. All of these muscles are those with high metabolic requirements. In other words, the body may only store thiamine in the muscle for 2-3 weeks with biological thiamine half-life for 9-18 days (Sica 2007). Therefore, the duration of this study was 28 days, adjusting to the thiamine uptake in muscle.

Based on the results of this study, nonparametric difference test on patients' blood pressure data between pre and post treatments in control and treatment groups at baseline and final data showed significant result. This significance may indicate that the changes in the patients' blood pressure towards normal conditions are the parameter to evaluate patients' compliance in stage II heart failure therapy in which the blood pressure is needed to prevent the occurrence of more severe heart failure. Left ventricular systolic pressure dysfunction is a common feature of patients with heart failure. Generally, the result of the assessment may be evaluated from the changes in patient's blood pressure (Chavey 2012).

One of the parameters to evaluate heart function is ejection fraction (EF). Normal rate of the EF is > 60%. EF less than 40% indicates the decrease of heart function. The indication of applying echocardiography is when the patient has heart valve problem or when there is heart murmur in physical examination. Heart murmur is a condition when there is a suspicion of congenital heart problem, evaluation of aortic condition, pulmonary hypertension, pulmonary embolism, heart enlargement on examination of the thoracic image or on physical examination, pericardial effusion, heart failure, and the presence of arrhythmia. Echocardiography is also used to assess the presence of intra cardiac initiator, evaluation heart function on drug use, and as guidance in pericardial function, pacemaker and others.

Based on the results of the study, comparative test result between the baseline data from treatment and control

groups observed by the BiPlane method showed not significant result because this observational method is useful for evaluating left ventricular volume when the left ventricle is distorted by blood flow input. The emerging model is the profile of left ventricular endocardium in lateral resolution. Thus, sometimes, observers find it difficult to identify the epicardium contour in detail. However, in general, this method is able to describe heart muscle pieces according to the volume of the cylinder alignment and the depth of the heart muscle along the left ventricle. In addition, not significant pre comparative test result from the control and treatment group indicated random sampling method. The equality of baseline ejection fraction condition of the study samples may be used to ensure data homogeneity, minimize confounding variables, and maximally evaluate in post treatment observation.

CONCLUSION

The result of comparative test analysis of baseline data between treatment and control groups using Teich method showed significant result. This condition occurred because Teich method is able to evaluate the profile of heart function in the final state of systolic and diastolic parasternal long-axis, and apical shape. This method is helpful in suboptimal apical model condition because of the inadequate tracing of endocardial contour. This method is able to evaluate the occurrence of remodeling in the left ventricle.

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