EFFECT OF FURSULTIAMINE SUPPLEMENTATION ON LEFT VENTRICULAR EJECTION FRACTION (LVEF) IN GRADE III – IV HEART FAILURE PATIENTS

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ABSTRAK

Gagal jantung merupakan masalah yang sedang berkembang dan melibatkan lebih dari 20 juta individu di seluruh dunia. Terapi farmakologi yang telah banyak dipergunakan dalam manajemen gagal jantung merupakan terapi kombinasi diuretik, ACE-I, ARB, digitalis, beta bloker, MRA. Tujuan dari terapi tersebut adalah untuk perbaikan hemodinamika, modulasi neurohormonal dan elektrofisiologis jantung. Namun terapi tersebut tidak mampu memenuhi kebutuhan metabolisme jantung yang mengalami penurunan akibat kondisi gagal jantung. Suplementasi mikronutrien pada terapi standar gagal jantung dipercaya mampu memberikan efek sinergis dengan jalan memenuhi kebutuhan terhadap kofaktor dalam metabolisme energi jantung. Thiamin (vitamin B1) merupakan salah satu mikronutrien yang bekerja dalam membantu metabolisme energi jantung, sedangkan fursultiamine merupakan senyawa turunan thiamin yang memiliki daya penembusan sel yang lebih baik dibanding thiamin. Tujuan dari penelitian ini adalah untuk mengevaluasi efek suplementasi fursultiamine terhadap perbaikan fungsi jantung yang dinilai lewat peningkatan fraksi ejeksi ventrikel kiri (Left Ventricular Ejection Fraction/ LVEF). Hasil yang diperoleh adalah suplementasi fursultiamine bersama terapi standar gagal jantung mampu memberikan peningkatan nilai LVEF yang lebih besar bila dibandingkan dengan pasien yang hanya menerima terapi standar gagal jantung saja. ***(FMI 2015;51:101-105)***

Kata kunci: *fursultiamine, suplementasi, gagal jantung, fraksi ejeksi ventrikel kiri, LVEF*

ABSTRACT

Heart failure is a growing problem and affecting more than 20 millions people around the world. Pharmacology therapy that has been use for heart failure management are combination of diuretic, ACE-I, ARB, digitalis, beta blocker and MRA. The purpose of that therapy is to improve haemodynamic function, neurohormonal modulation, and cardiac electrophysiology. But they aren't able to fulfill the metabolic demand of the failing heart. Micronutrient supplementation along with standard combination therapy will create synergistic effect not only on haemodynamic function but also on cardiac energy metabolism. Thiamin (B1 vitamin) is one of micronutrients that be able to work on cardiac energy metabolism, where as fursultiamine is thiamin derifative which has better cell penetration than thiamin it self. The purpose of this reasearch is to evaluate the effect after fursultiamine supplementation on cardiac function measured by the improvement on left ventricular ejection fraction (LVEF). The result of this research shows that fursultiamine supplementation along with standard combination therapy can give higher LVEF improvement than the patient that receive standard combination therapy alone. ***(FMI 2015;51:101-105)***

Keywords: *fursultiamine, supplementation, heart failure, left ventricular ejection fraction*

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INTRODUCTION

Heart failure is a clinical syndrome characterized by inability of the heart to fulfill tissue oxygen demand. The failure appears as manifestation of abnormality of cardiac structure, function or both (Longo et al 2012). Heart failure has become a growing problem and affecting more than 20 millions individual around the world. Total prevalence on adult population on developing country has reach 2% and increasing together with age, it affects 6 – 10% of individual with more than 65 years of age. However there is no sufficient epidemiology data for heart failure patients in Indonesia (Fauzi 2009). The most heart failure classification system use nowadays is New York Heart Association Classification system (NYHA 1964), it classify heart failure into four different class (Class I – IV) based on clinical condition (fatigue, palpitation, dyspnea, anginal pain) and the ability on physical activities. Heart failure severity increase together with the class, it means that the most severe heart failure is the fourth class (Longo et al 2012).

Heart failure will cause metabolic remodeling marked by progressive reduction on adenosine triphosphate (ATP) production in myocit. It controlled by energy sensor such as adenosine monophosphate (AMP) which cause changing in many protein phosphorylation

statuses to fulfill ATP demand as fast as possible. Meanwhile, the changing also appear on transcription factor and co-activator such as peroxisome proliferator - activated receptor γ (PPARγ), co-activator 1 (PGC – 1a), which arrange coordinated long-term remodeling on synthesis and ATP use pathway. The main substrate on adult human cardiac ATP synthesis is free fatty acid (FFA) oxidation, if there is failure or downfall on those pathway, it will activate phosphotransferase (Creatine Kinase (CK) and Adenylate Kinase (AK)) and glycol-lytic or gluconeogenesis pathway.

At decompensated heart failure there will be reduction on ATP synthesis from phosphotransferase pathway, as if the heart failure severity increase (NYHA class IV), ATP synthesis will be much lower and the main substrate will be no longer from FFA, but glucose (glycolytic pathway). The energy production will no longer be able to compensate the myocardium energy demand, so it will cause disturbance on the failing cardiac contractility recovery (Ingwall 2009).

Micronutrient supplementation (thiamin) along with heart failure standard combination therapy will be able to create synergistic effect as cofactor on energy metabolism (Soukoulis et al 2009). There are three biochemical form of thiamin, which is thiamin mono-phosphate, thiamin diphosphate (thiamin pyrophos-phate) and thiamin triphosphate. Thiamin pyrophos-phate is the major compound, where as thiamin triphosphate is the minor (Lonsdale 2006). Thiamin pyrophosphate serves as a coenzyme in the oxidation – reduction reaction, particularly glucose metabolism, pentose shunt, and the citric acid cycle, also function in mitochondrial oxidative decarboxylation and more than 24 enzymatic reactions in the body, primarily as a coenzyme in the reaction catalyzed by the enzyme dehydrogenase pyruvat, alpha-ketoglutarate dehydro-genase and transketolase. Fursultiamine have better bioavailability and penetration into the cell than thiamin. After entering into the blood vessels, disulfide compounds will be more easily reduced to thiamin with the help of cysteine or glutathion (Bettendorf 2012), so it's expected that fursultiamine supplementation will be able to improve energy metabolism and heart function. Measurements parameter using LVEF have been selected because it is one of prognostic indicators associated with mortality, where a decrease in LVEF ≤ 30% will have a big risk of mortality in the amount of 37.26% (from a total of 1535 patients with heart failure) (Varadarajan & Pai 2003). Every 10% decrease in LVEF below 45%, will lead to an increased risk of mortality by 39%. The cause of mortality is sudden death, heart failure-related death, MI, stroke (Solomon et al 2005). Studies evaluating the effects of supplementation on LVEF fursultiamine has never done before, therefore, this study aims to look at the effect of supplementation fursultiamine to increase LVEF in patients with heart failure, compared to patients who only get standard heart failure therapy alone.

MATERIALS AND METHODS

The study was using an open label design performed in Cardiology Department of Dr. Soetomo hospital starting on July to December 2014. This study was approved by Dr. Soetomo ethical committee (Ethical Clearance) 412/PankeKKE/X/2014. Test subjects included in this study were 15 patients in the control group and 15 patients in the treatment group. The control group getting standard combination therapy for heart failure during the seven days, while the treatment group getting standard combination therapy and supplementation fursultiamine for seven days.

Inclusion criteria were patients with male/female aged between 40-60 years, diagnosed with heart failure (NYHA III - IV) either newly diagnosed or who have long suffered from heart failure, heart failure receiving standard therapy combination, baseline LVEF < 40% and has been signed patient consent form. The patients were excluded if suffering from malignant diseases, myeloproliferative, acute infection, thyrotoxicosis, kidney failure, diabetes mellitus and patients who regularly take vitamin or multivitamin before. Patients will be dropped out from the study if experienced hypersensitivity to fursultiamine, go home before the seven-day intervention and patients who withdrew from the study. Measurement of LVEF measured using echocardiography at baseline (baseline LVEF) and after seven days of treatment. Control and treatment LVEF data were statistically analyzed using Mann Whitney (Dahlan 2008).

RESULTS

The study involving thirty patients and divided into two groups: a control and treatment group of fifteen patients. Patient characteristic data in Table 1 shows the percentage of male and female patients were the same, 50%, whereas according to age, the percentage of patients aged 40-50 years is 50% and aged 50-60 years also by 50%. The etiology of heart failure patient is OMI CHD by 20%, ICM 46.7%, DCM by 20% and severe AR + MR were 13.3%.

LVEF data after seven days (control group) are shown by table 2, while the initial LVEF and after seven days of standard combination therapy and fursultiamine shown by Table 3. The value of the control group

baseline LVEF was 22% ± 3.94%, with a minimum value of 20% and a maximum value of 33%, while the baseline LVEF value of the treatment group was 23% ± 4.34%, with a minimum value of 17% and a maximum value of 35%. After seven days, LVEF measured again and showed that only seven patients in the control group experienced an increase in LVEF of 1-2%, seven other patients did not experience an increase and one patient experienced a decrease in LVEF of 10%, an increase in LVEF was not significant ($p > 0.05$). The treatment group experienced an increase in LVEF was significantly ($p < 0.05$), LVEF increased by 9% ± 3.8%, with a minimum value of 4% and a maximum of 17%. Mann Whitney test between control and treatment groups showed differences significant increase in LVEF between the control and treatment groups ($p < 0.05$).

DISCUSSION

The decline in LVEF (systolic dysfunction) in heart failure is influenced by several things, namely the etiology of heart failure such as Coronary Artery Disease (CAD), aortic regurgitation, Cardiomyopathy, gender, where the number of men who have heart failure systolic dysfunction is greater when compared with women, presence or absence of left bundle branch block (LBBB) and potassium levels at heart failure onset (Lee et al 2009). A total of six patients (three of three from the control group and the treatment group) had coronary heart disease etiology, twenty patients (ten patients from the control group and ten patients from the treatment group) has the etiology of cardiomyopathy, and four patients (two patients from the control group and two treatment groups) had aortic regurgitation etiology. The etiology differences affect standard therapy received by each - each patient, therefore each - each patient receiving standard therapy according to different etiology heart failure. Differences in etiology and standard therapy can lead to variability in the data, therefore this study using open clinical trials without randomization, so that researchers can choose the subject of research and minimize the variability of the study subjects.

The magnitude of the increase (difference) baseline LVEF and the seventh day of the two groups were compared and statistically tested using Mann Whitney test and get the result that there are differences in the increase in LVEF from the control group and the treatment group, in which an increase in LVEF of treatment groups are larger when compared with the control group, thus fursultiamine considered able to help improve the cardiac contractility function.

Table 1. Patients' characteristics

Characteristics	Control group (n = 15)	Treatment group (n = 15)	%
Age (years)			
40 - 50	7	8	50
50 - 60	8	7	50
Sex			
Male	8	7	50
Female	7	8	50
Diagnosis			
ACD OMI + DCFC III/IV	3	3	20
ICM + DCFC III/IV	7	7	46.7
DCM + DCFC III/IV	3	3	20
Severe AR + Intermediate MR + DCFC III/IV	2	2	13.3
Baseline LVEF value			
10 – 20%	2	3	16.7
21 – 30%	12	11	76.7
31 – 40%	1	1	6.7
Standard therapy			
F + C + D + S + A	1	1	6.7
F + C + D + S + A + B + Is	2	2	13.3
F + C + S + B + Ir + Is	1	1	6.7
F + C + S + B + Is	1	1	6.7
F + C + S + B + Is + A	1	1	6.7
F + C + S + B + A	1	1	6.7
F + C + S + D + B	1	1	6.7
F + C + CPG + A	1	1	6.7
F + C + A	2	2	13.3
F + C + A + S	2	2	13.3
F + C + B + S	2	2	13.3
Blood pressure (mmHg)			
Systolic	110 ± 21	120 ± 18.8	
Diastolic	70 ± 9.48	70 ± 13.2	
Heart Rate (x/minute)	104 ± 22.67	100 ± 8.97	
Respiration Rate/RR (x/minute)	24 ± 6.22	24 ± 2.81	

Notes:
ACD = Artery Coronary Disease
DCM = Dilated Cardiomyopathy
MR = Mitral Regurgitation
C = Captopril
A = ASA
S = Spironolactone
Is = ISDN
ICM = Ischemic Cardiomyopathy
AR = Atrial Regurgutation
F = Furosemide
CPG = Clopidogrel
D = Digoxin
Ir = Irbesartan
B = Bisoprolol

Table 2. Control group LVEF value

Patient no	Age (Years)	Sex	Baseline LVEF %	Seven days LVEF %	Delta %
1	56	L	20	22	2
2	60	L	21	22	1
3	42	L	33	23	-10
4	45	L	24	26	2
5	58	L	27	28	1
6	43	L	20	21	1
7	47	L	29	30	1
8	57	P	21	21	-
9	58	P	29	29	-
10	55	L	25	25	-
11	45	P	23	24	1
12	46	P	22	22	-
13	52	P	21	21	-
14	46	P	22	22	-
15	57	P	21	21	-

Table 3. Treatment group LVEF value

Patient NO	Years (Age)	Sex	Baseline LVEF %	Seven day LVEF %	Delta %
1	45	L	20	24	4
2	44	P	25	42	17
3	52	L	23	39	16
4	57	L	22	26	4
5	56	P	22	31	9
6	58	P	30	40	10
7	46	P	23	30	7
8	46	L	17	25	8
9	50	P	22	30	8
10	45	P	20	30	10
11	40	L	35	46	11
12	55	L	25	39	14
13	45	P	21	30	9
14	53	L	25	33	8
15	56	P	25	32	7

These results are similar to previous studies conducted by Shimon et al (1995) and Schoenenberger et al (2012), where the two studies also suggest that the standard heart failure therapy without thiamine supplementation was not able to improve LVEF significantly, whereas patients receiving standard heart failure therapy along with thiamin supplementation were able to increase LVEF were more significant.

LVEF is a prognostic indicator related mortality, where a decrease in LVEF ≤ 30% will have a big risk of mortality in the amount of 37.26% (from a total of 1535 patients with heart failure) (Varadarajan & Pai 2003). Every 10% decrease in LVEF below 45%, will lead to an increased risk of mortality by 39%. The cause of mortality is sudden death, heart failure-related death, MI, stroke (Solomon et al 2005). TPP is able to provide favorable hemodynamic effects and restore energy balance myocardial ischemic myocardial infarction and cardiac arrest (Soukoulis et al 2009).

Increase in LVEF greater after supplementation fursultiamine possible because fursultiamine is able to work directly on cardiac myocytes with the increased production of energy which is then followed by an increase in cardiac function. The decline in LVEF can be used as a powerful predictor of view of worsening heart failure and mortality conditions, so that the increase in LVEF after fursultiamine supplementation can reduce the mortality rate of patient's heart failure (DiNicolantonio et al 2013). Although these results were statistically significant, but the increase in LVEF is said to be clinically significance if LVEF can return to a normal rate which is ≥ 40%. Data resulting from an increase in LVEF above shows that there are no research subjects in the control group with LVEF ≥ 40%, while the treatment group contained three study subjects were able to achieve LVEF ≥ 40%, which is 42%, 40% and 46%.

This study has some weaknesses such as its short time of the study, so that the effect of supplementation on mortality and fursultiamine re-hospitalize cannot be seen, therefore, required a similar study with a longer period of time, using outpatients by using the oral route. As mentioned above that micronutrients that can contribute to improve cardiac metabolism were not only thiamin and its derivatives, but also other micronutrients such as L-carnitine, taurine and coenzyme Q-10, but no studies have compared the effects of thiamine supplementation or fursultiamine with the effect of another micronutrient supplementation, so it can not be seen the type of micronutrient supplementation which are able to provide greater increase in LVEF, therefore, other studies are also needed to compare the effects of supplementation of each of these micronutrients to the increase in LVEF.

In addition to the measurement of LVEF, we are monitoring other parameters include blood pressure (BP), pulse and respiration rate (RR) of each research subject from baseline to day seven studies. Of the three parameters, BP and pulse parameters are fluctuative, b ut at the end of the study (the seventh day) the pulse tend to be stable <100x/min, while the blood pressure in the range of ≤ 140/90 mmHg. According to the American Heart Association (AHA) in 2007, the target blood pressure for patients with heart failure is < 120/80 mmHg, from thirty patients, twenty-seven patients had BP ≤ 120/80 mmHg, while three other patients had TD ≤ 140/90, BP and pulse monitoring in patients with heart failure function to see the progression of the disease and the prevention of other cardiovascular complications, despite that the use of combination antihypertensive in heart failure patients need close monitoring to avoid hypotension. Parameters RR patients tend to exceed the normal value is > 20x/min at baseline, but at the end of the study (day seven) parameter RR is the normal range is < 20x/min.

Increasing the value of RR in the beginning of the study was probably due to a buildup of fluid in the lungs, either in the form of acute lung edema (ALO) and pleural effusion. All the patients in the control group and the treatment group got furosemide pump therapy with a dose of 5 mg/hour at the start of the study which serves to remove the fluid buildup. If the buildup of fluid in the lungs has been lost, it can be returned to normal RR, evident after treatment with furosemide, shortness of breath of the patients was reduced and the value of was RR back to normal.

CONCLUSION

Standard heart failure therapy along with supplement-ation fursultiamine is able to improve LVEF greater than standard heart failure therapy alone.

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