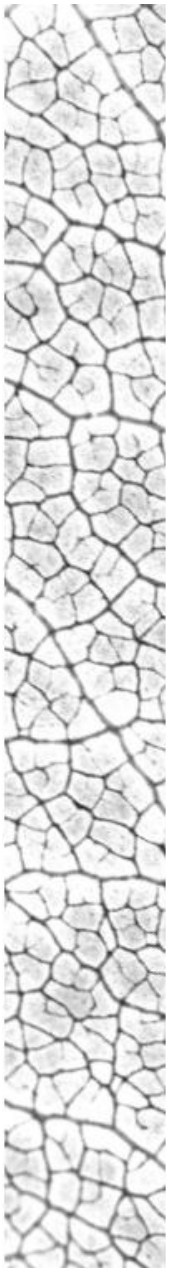

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Potention of L-carnitine supplementation on changes in ejection fraction and left ventricular dimension in case of dilatative cardiomyopathy in children

Wahyu Wibowo [1], Mahrus A Rahman [1*], I Ketut Alit Utamayasa [1]

[1] Department of Child Health, Faculty of Medicine, Universitas Airlangga - Dr. Soetomo Teaching Hospital, Surabaya Surabaya 60131, INDONESIA
*Corresponding author: mahrus_rahman@yahoo.com

Abstract

Background: Cardiomyopathy is a rare cardiac muscle disease with poor prognosis and high mortality. The main goal of dilated cardiomyopathy therapy is to restore and maximize cardiac function, but to date no medication has met these criteria. The use of oral L-carnitine as a dilated cardiomyopathy therapy has a potency to gives good results in restore and maximize cardiac function. **Purpose:** Knowing the effect of L-carnitine supplementation in children with cardiomyopathy on ejection fraction and left ventricular dimensions. **Method:** Experimental studies with randomized control trial design were conducted for one year, to determine the effect of L-carnitine in the experiment by performing twice the ejection fraction measurements and left ventricular dimensions performed before and after the administration of L-carnitine for 1 month. This research does not use blind method. Sampling was done randomly with comparison control. Different test was conducted with Saphiro-Wilk followed by T-test. **Result:** Fourteen samples were analyzed. In the treatment group, an increase in ejection fraction (p = 0.033), decreased left ventricular systolic phase end dimension (p = 0.043) and at the end of diastolic phase (p = 0.170). There was a significant difference in the increase of ejection fraction between treatment group and control group (p = 0,035), but no significant difference was found between treatment group and control group of final phase of systole (p = 0,228) and final phase of diastol (p = 0,704). **Conclusion:** L-carnitine supplementation in children with dilatative cardiomyopathy can increase ejection fraction, but not decrease the left ventricular dimension.

Keywords: dilated cardiomyopathy, L-carnitine, ejection fraction, left ventricular dimension

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INTRODUCTION

Cardiomyopathy is a rare heart muscle disease with a poor prognosis and high mortality (Rong, et al. 2019). This heart muscle disease can affect blood flow throughout the body (Laswati, et al. 2018). Incidence varies between 2-8 cases every 100,000 to 17.2 cases per 100,000 population in all age groups 1 In most cases, no cause can be identified and the disease is considered idiopathic (Kaski, et al. 2010). About 40% of children with symptoms of cardiomyopathy need a transplant or will die within the first 2 years (Lipshultz, et al. 2003).

The main goal of dilatative cardiomyopathy therapy is to restore and maximize cardiac function, but until now there has been no drug that meets these criteria. Conventional therapies that are commonly used are diuretics, angiotension-converting enzymes / ACE inhibitors, and digoxin. This diuretic is only limited to reduce symptoms, ACE inhibitors such as in children are still limited, digoxin does not reduce mortality and preferably use intravenous inotropic use in children (Abdullsattar Saad, 2007).

Levocarnitine (L-carnitine) is an essential amino acid derivative that has an important role in heart muscle metabolism. More than 90% are found in skeletal muscle cells and heart muscle cells. L-carnitine acts as a carrier of acyl co-enzyme A (CoA) needed in beta oxidation to produce energy for the heart muscle in the form of Adenosine Triphosphate (ATP) to carry out its activities. In dilatative cardiomyopathy there is an accumulation of toxic organic intermediates that are toxic in cells. This causes a reduction in the amount of L-carnitine (Helton, et al. 2000).

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Table 1. Difference between the initial and final ejection fraction in the treatment group (L-carnitine) and the initial and final ejection fraction in the control group

Variable	Early Average (SD)	End Average (SD)	*p*
Ejection Fraction			
Treatment	37,087 (14,553)	44,811 (17,981)	0,033
Control	44,627 (15,932)	44,197 (17,634)	0,837

Table 2. Differences between initial and final left ventricular dimensions in the treatment group (L-carnitine) and initial and final left ventricular dimensions in the control group

Variable	Early Average (SD) (cm)	Early Average (SD) (cm)	p
Left Ventricular Dimension (*end sistole*)			
Treatment	4,624 (1,397)	4,140 (1,525)	0,043
Control	4,233 (1,405)	4,056 (1,624)	0,284
Left Ventricular Dimension (*end diastole*)			
Treatment	5,589 (1,264)	5,294 (1,361)	0,170
Control	5,356 (1,229)	5,167 (1,005)	0,398

L-carnitine supplementation is expected to increase PI3K levels in the heart muscle so that it will improve contractility of the heart muscle and will also increase glucose metabolism and long-chain fatty acid metabolism which will ultimately increase the amount of energy in the form of ATP. Energy in the form of ATP will improve heart muscle metabolism so that contractility and elasticity will increase. With increasing contractility and elasticity of the heart muscle, there will be an increase in the ejection fraction and a decrease in the dimensions of the left ventricle. In addition to producing energy in the form of ATP, oxidation of this long chain fatty acids will also reduce the levels of these long chain fatty acids and reduce the levels of acyl-carnitine so that it will form protection in the form of membrane lipids and protein enzymes so that there is a potential restoring of rest of the heart muscle which will ultimately increase ejection fraction and decrease the dimensions of the left ventricle (Helton, et al. 2000; Tilahun, et al, 2015).

At the hospital Dr. Soetomo, Indonesia is still giving captopril, furosemide, and digoxin therapy to patients with dilatative cardiomyopathy. Evaluation of changes in ejection fraction and changes in left ventricular dimensions to assess the effect of L-carnitine supplementation by increasing contractility and elasticity of the heart muscle is expected to improve or improve the clinical condition of patients with dilatative cardiomyopathy.

METHOD

This type of research is experimental with a randomized control trial design research design, to determine the effect of treatment on the experiment by making two observations of variables that were made before and after treatment. This study did not use the blind method. The research lasted for 10 months.

Population and Sample

Sampling is done randomly with a comparison control. The subjects of this study were children aged 2-18 years who suffered from dilatative cardiomyopathy in the Outpatient and Pediatric Inpatient Care Department of Cardiology at Dr. Soetomo Hospital, Indonesia, who met the inclusion and exclusion criteria. The study was divided into two groups. The first group (treatment) were children with conventional therapy plus L-carnitine supplementation 100 mg / kg / day and the second group were children with conventional (control) therapy. A total of 14 samples were examined for homogeneity in sex, age and weight.

Data analysis

The diagnosis of dilatative cardiomyopathy is determined based on the results of echocardiography performed and read by a child cardiology consultant Dr. Soetomo, Indonesia. The analysis used is descriptive analysis to determine the physical characteristics of the research subjects and independent sample T-Test to analyze differences in the ejection fraction and changes in the dimensions of the left ventricle as well as the difference in the ejection fraction and the difference in left ventricular dimension changes, the two groups (01 and 01 ‘, 02 and 02 ‘). Data were analyzed using 95% confidence level (α = 0.05).

RESULTS

In this study the initial and final ejection fractions in the treatment group (L-carnitine) and the control group as shown in **Table 1**. From the data shown in **Table 1** it was found that there were significant differences between the initial and final ejection fractions in the treatment group (L- carnitine) whereas in the control group no significant differences were found. The value of each p = 0.033 for the value of the ejection fraction in the treatment group (L-carnitine) and p = 0.373 in the control group.

In this study the initial and final left ventricular dimensions in the treatment group (L-carnitine) and the control group as shown in **Table 2**.

From the data shown in **Table 3**, it was found that there was a significant difference / reduction in the left ventricular dimension of the late end systole (end systole) with the end of the treatment group (L-carnitine), but no significant difference / decrease in the left ventricular dimension of the final phase systole (end systole) beginning with end in the control group. But

Table 3. Difference in Changes in Ejection Faction and Left Ventricular Dimensions in the Treatment Group (L-Carnitine) and in the Control Group

Deviation	Group		*p*
	Treatment	Control	
Ejection Fraction Left Ventricular Dimension:	7,724 ± 7,384	-0,430 ± 5,291	0,035
End systol (*end sistole*)	-0,484 ± 0,499	-0,177 ± 0,398	0,228
End diastol (*end diastole*)	-2,943 ± 0,500	-0,189 ± 0,516	0,704

there was no significant difference between the dimensions of the initial left ventricle (end diastole) with the end in each treatment group (L-carnitine) or in the control group. The value of p = 0.043 for the value of the dimensions of the left ventricle (end systole) and p = 0.170 for the value of the dimensions of the left ventricle (end diastole).

In this study the difference in changes in the ejection fraction and the dimensions of the left ventricle in the treatment group (L-carnitine) and the control group as shown in **Table 3**.

From the data shown in **Table 3** it was found that there were significant differences between the ejection fraction differences in the treatment group (L-carnitine) compared to the control group with a p value = 0.035. But there was no significant difference in the difference between the dimensions of the left ventricular end systole (end systole) and at the end of diastole (end diastole) in each treatment group (L-carnitine) and the control group. The value of p = 0.228 for the value of the difference in the dimensions of the left ventricle at the end of systole (end systole) and p = 0.704 for the value of the dimension of the left ventricle at the end of diastole (end diastole).

In this study, there were no data on the incidence of intolerance in the form of diarrhea, nausea, vomiting and headaches as well as side effects in the form of fish odor after L-carnitine administration for 1 month.

DISCUSSION

In this study, there was a significant increase in ejection fraction after L-carnitine supplementation in the treatment group (L-carnitine), but in the control group there was no increase in ejection fraction. These results are in accordance with several studies that have been done before that look at the effect / effect of adding L-carnitine supplementation to the increase in ejection fraction.

Research on children with dilatative cardioiopathy aimed at looking at the ejection fraction after administration of L-carnitine with a dose range of 14 - 455 mg / kg / day conducted for 2 weeks to 1 year and the results showed an increase in ejection fraction in the group given additional L-supplementation carnitine is significantly compared to the control group who received standard furosemide therapy, ACE inhibitors, digoxin, β blockers and Ca antagonists 6. Helton's study is different from this study in standard therapy and the dose of L-carnitine used and the duration of L-carnitine administration.

In this study, there was a significant decrease in left ventricular dimension in the final phase of systole after L-carnitine supplementation for 1 month in the treatment group (L-carnitine), but there was no significant difference when comparing the difference / decrease in left ventricular dimension when systole between the treatment group with the control group. Different results obtained in the dimensions of the left ventricle in the final phase of diastole, ie no significant reduction was found in each treatment group (L-carnitine) and the control group. The difference in the decrease in left ventricular dimension when diastole between the treatment group and the control group was also not significant.

Previous studies in Egypt involving 14 children with dilatative cardiomyopathy looked at left ventricular function and serum L-carnitine levels between the treatment and control groups. The study was conducted for 3 months by giving additional L-carnitine to the treatment group at a dose of 100 mg / kg-weight / day. After 3 months of administration of L-carnitine, the result was a significant increase in the ejection fraction and a significant reduction in the left ventricular dimension of the final phase systole and the final phase of diastole. Kotby's research results are different from this study because the administration of L-carnitine is longer (3 months)(Abd, 2006)..

The oxidation of fatty acids by L-carnitine is the process that underlies the increased energy in the form of ATP in the heart muscle so that the contraction unit of the heart muscle increases (Ferrari, et al. 2004).L-carnitine also plays a role in increasing blood flow to the heart muscle that ischemia thereby preventing the accumulation of toxic metabolites (Morano, et al. 2007). Ischemia can occur in a variety of disease statuses and often occurs in various surgical procedures such as in the process of vascular surgery, although in children the risk level is lower than parents (Putri, & Hidajah, 2019. Lukiswanto, ewt al. 2017). From the results of an endomyocardial biopsy taken from the heart of a chronic heart failure patient, it is found that there is a relationship between decreased ATP concentrations with impaired contractions and relaxation (Ferrari, et al. 2004).

From the results of this study found a significant increase in the ejection fraction after administration of L-carnitine supplementation for 1 month in the treatment group compared to the control group. For the left ventricular dimension of the final systole phase there was no significant decrease after 1 month of L-carnitine supplementation in the treatment group compared to the control group, also the dimension of the left ventricle of the final phase of diastole was found to be insignificant reduction after L-carnitine supplementation for 1 month in the treatment group compared to the control group.

Researchers suspect that L-carnitine supplementation for 1 month in children with dilatative

cardiomyopathy has not been able to show an inhibitory effect on remodeling in heart muscle in children with dilatative cardiomyopathy. From previous studies stated that L-carnitine will show an inhibitory effect on remodeling of the heart muscle after being given for 2 to 12 months (Abd, 2006)

CONCLUSION

L-carnitine supplementation in children with dilatative cardiomyopathy can increase the ejection fraction, but does not decrease the left ventricular dimension.

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