Effect of Carnitine Supplementation in Pediatric Patients with Left Ventricular Dysfunction

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Abstract

Carnitine is an essential amino acid involved in transporting fatty acids across the mitochondrial membrane. Fatty acids are a primary source of energy for the myocardium. Studies in adults demonstrated decreased carnitine levels in the ischemic myocardium, but subsequent exogenous carnitine supplementation showed improvement of myocardial metabolism and left ventricular function. However, only limited data regarding carnitine is available in pediatrics. A single-center retrospective, paired data study was conducted. Patients < 18 years, left ventricular ejection fraction (LVEF) < 55% by echocardiography and had received at least 7 days of oral or intravenous carnitine supplementation between January 2018 and March 2021 are included in the study. Several endpoints and covariates were collected for each patient; before, one week after, one month after, and six months after carnitine supplementation. Univariate analysis consisted of an analysis of variance (ANOVA), followed by an analysis of covariance (ANCOVA) to model LVEF while adjusting for other variables. 44 patients included in the final analyses. LVEF significantly improved from 50.5–56.6% ($p < 0.01$). When LVEF was adjusted for other interventions (mechanical ventilation, afterload reduction, diuretic therapy, spironolactone), the estimated means demonstrated a significant increase from 45.7–58.0% ($p < 0.01$). Free carnitine level increased significantly ($p = 0.03$), and N-terminal-pro-brain-natriuretic peptide ($p = 0.03$), creatinine ($p < 0.01$), and lactate ($p < 0.01$) all significantly decreased over the study period. Carnitine supplementation in pediatric patients with left ventricular systolic dysfunction may be associated with an increase in LVEF and improvement in laboratory markers of myocardial stress and cardiac output.

Introduction

Carnitine is an essential amino acid that is synthesized endogenously in the liver, kidney, and brain from lysine or methionine. Carnitine plays an important role in transporting fatty acids across the mitochondrial membrane [1]. Fatty acid serves as the primary source of energy for cardiac muscle and other vital organs [2]. In adults there are studies that have demonstrated significantly lower myocardial carnitine levels during periods of ischemia. These studies also noted that exogenous carnitine supplementation was associated with improvement in myocardial metabolism and left ventricular function [3, 4]. In the pediatric population, however, there is limited data regarding the effect of carnitine on myocardial function.

Loomba et al conducted a systematic review and meta-analysis study of studies regarding carnitine supplementation in the pediatric population and found only 6 studies with total of 144 patients [5]. They found a statistically significant increase in LVEF and shortening fraction after carnitine supplementation.

The primary aim of this study was to characterize LVEF at various timepoints before and after carnitine supplementation in pediatric patients with left ventricular dysfunction. Secondary aims included characterizing other echocardiographic, laboratory, and hemodynamic indices at similar timepoints.

Methods

Study design

This was a single center retrospective study following patients longitudinally. Data was collected for predefined variables at each time point for comparison between timepoints of the same patient.

This study was approved by the local institutional review board and is in concordance with the Helsinki Declaration.

Patient identification

The following inclusion criteria were used for this study: 1) pediatric patients (under 18 years of age); 2) carnitine supplementation initiated while admitted to Advocate Children's Hospital in Oak Lawn, IL; 3) left ventricular dysfunction defined by ejection fraction (EF) < 55% documented by echocardiography; 4) available echocardiographic images from which an ejection fraction could be estimated; 5) received at least 7 days of carnitine either orally or intravenously. Patients who received carnitine supplementation initiated while having normal LVEF (> = 55%) and those in whom carnitine supplementation was initiated while on mechanical circulatory support were excluded from this study.

Variables of interest

LVEF was the primary endpoint of this study. Other echocardiographic findings (shortening fraction, strain), laboratory findings (N-terminal-pro-brain-natriuretic peptide, troponin, creatinine I, blood urea nitrogen, aspartate aminotransferase, alanine aminotransferase, and lactate), and hemodynamics (heart rate, systolic blood pressure, diastolic blood pressure, cerebral near infrared spectroscopy, and renal near infrared spectroscopy) were collected for secondary endpoints. Other covariables, felt to influence LVEF, were also collected. These included the dose of carnitine (daily dose per kilogram), intravenous carnitine (yes/no), mechanical ventilation (yes/no), vasoinotrope score, afterload reduction medications (yes/no), diuretics (yes/no), spironolactone (yes/no), and total and free carnitine levels. Data collection timepoints included immediately prior to carnitine supplementation, one week after carnitine supplementation, one month after carnitine supplementation, and six months after carnitine supplementation.

Statistical analysis

Normalcy of distribution of data were assessed using skewness and kurtosis. For continuous variables, data were reported as mean and standard deviation if normally distributed and as median and range if not normally distributed. Descriptive data were reported as absolute frequency and percent. Unadjusted, univariate analyses for continuous variables were compared across timepoints using a repeated measures analysis of variance analysis. Unadjusted, univariate analyses for descriptive variables were conducted using a Fisher's test.

As change in LVEF was of primary interest, an adjusted analysis was conducted using a repeated measures analysis of covariance. LVEF was the dependent variable in this model with need for mechanical ventilation, afterload reduction, diuretic therapy, and spironolactone therapy entered as

independent variables. A Bonferroni correction was used. Mean estimates for LVEF were then tabulated for each timepoint.

Next, a linear regression analysis was conducted with the absolute ejection fraction as the dependent variable. Need for mechanical ventilation, afterload reduction, diuretic therapy, and spironolactone therapy were entered as independent variables. Each data point was treated as a separate case and the time point at which that data was collected was also entered as an independent variable. Time was entered in weeks with baseline being 0, 1 week being 1 week, 1 month being 4 weeks, and 6 months being 24 weeks. The purpose of this particular analysis was to determine the association of time with ejection fraction.

Finally, a continuous variable was created to represent the total change in LVEF between the baseline and 6-month follow-up data (LVEF at 6-months minus LVEF at baseline). This was then used as the dependent variable in a paired linear regression analysis with all baseline and 6-month follow-up variables with a p-value of less than 0.20 by univariate analyses entered as independent variables. The regression was conducted using backwards elimination with a likelihood ratio method of variable selection. This strategy allowed for both a priori selection and stepwise selection to help result in a robust, reproducible model.

All statistical analyses were conducted using SPSS Version 23.0. A p-value of 0.05 was considered statistically significant. Any use of “significant”, “significantly”, or “significance” in this manuscript refers to statistical significance unless otherwise explicitly stated.

Results

Cohort information

A total of 44 patients were included in the final analyses. There were 25 males and 19 females in the group. Neonates were defined as less than 1 month of age, infants between 1 month to 1 year of age, and children between 1 year and 18 years of age. There were 27 total patients with primary diagnosis of congenital heart disease (CHD) (Table 1). Table 2 demonstrates the breakdowns of 27 patients with primary diagnosis of CHD.

Table 1
Demographics of patients based on age and CHD status

	Male (n = 25)	Female (n = 19)
Neonates (< 1 month)	12	11
Infants (1 month – 1 year)	4	5
Children (1–18 year)	9	3
non-CHD diagnosis	9	8
CHD diagnosis	16	11

Table 2
Breakdowns of patients with primary diagnosis of congenital heart disease

Primary diagnosis of CHD	Number of patients (n = 27)
D transposition of the great arteries	6
Coarctation of aorta	5
Pulmonary atresia	3
Truncus arteriosus	3
Total anomalous pulmonary venous return	2
Ventricular septal defect	2
Tetralogy of Fallot	2
Taussig Bing anomaly	1
Congenital cardiomegaly	1
Critical pulmonary stenosis	1
Dilated aortic root (Marfan)	1

Mean age at time of carnitine initiation was 28 months (2 years). There was a large range of age, however, with neonates to 17-year-olds in the cohort. Mean weight at first dose was 14.6 kg. The daily dose of carnitine on initiation was 65.4 mg/kg/day (Table 3).

Table 3
Means and standard deviations of age, weight at 1st dose of carnitine, dose of carnitine, and the blood levels of carnitine

	Mean	Standard Deviation	Median	Minimum	Maximum
Age (Months)	28.9	58.5	0	0	206
Weight at 1st dose of carnitine (kg)	14.6	27.6	3.8	1.95	133
Dose of Carnitine (mg/kg/day)	65.4	31.1	60.1	7.3	110.4
Total carnitine level before supplementation (umol/L)	44.9	27.8	34	10	121
Free carnitine level before supplementation (umol/L)	29.1	20.2	20	7	89

Concomitant interventions

There was attrition throughout the follow-up due to varying follow-up status. At the baseline timepoint there were 44 patients, at the 1-week timepoint there were 33, at the 1-month follow-up there were 24, and at 6-months follow-up there were 17. Interventions, other than carnitine, were divided into five large groups: mechanical ventilation, vasoactive medications (Epinephrine, Norepinephrine, Dopamine, Dobutamine, Milrinone), afterload reduction, diuretic therapy, and Spironolactone. Spironolactone was placed in a separate group as it isn't used for diuretic effect in this population at our institution. Tables 4 and 5 summarize the proportion of patients who received various interventions at each time-point. Mechanical ventilation was used less at 6-months after carnitine initiation when compared to earlier timepoints ($p < 0.01$). Afterload reduction was increasingly used over the study period ($p < 0.01$). Diuretic and Spironolactone use did not significantly change over the study period (Table 4). Vasoactive support is described as vasoinotrope score in Table 5. Vasoactive medications were also decreasingly used throughout the study period ($p = 0.04$).

Table 4
Descriptive variables by timepoints

	Baseline (N = 44)	1-week after carnitine initiation (N = 33)	1-month after carnitine initiation (N = 24)	6-months after carnitine initiation (N = 17)	p-value
Mechanical ventilation	22 (50.0%)	10 (30.3%)	2 (8.3%)	0 (0.0%)	< 0.01
Afterload reduction	9 (20.5%)	10 (30.3%)	10 (41.7%)	12 (50.0%)	< 0.01
Diuretics (Furosemide, chlorothiazide, bumetanide)	18 (40.9%)	23 (69.7%)	12 (50.0%)	8 (47.1%)	0.08
Spironolactone	9 (20.5%)	10 (30.3%)	10 (41.7%)	8 (47.1%)	0.13

Table 5
Continuous variables by timepoints

	Baseline	1-week after carnitine initiation	1-month after carnitine initiation	6-months after carnitine initiation	p-value
LVEF (%)	50.5 ± 21.0	51.7 ± 16.6	52.8 ± 14.3	56.6 ± 10.3	< 0.01
Left ventricular shortening fraction (%)	28.5 ± 11.5	28.9 ± 8.4	27.7 ± 8.9	29.8 ± 6.5	0.10
Left ventricular global longitudinal strain (%)	-9.3 ± 5.9	-17.2 ± 7.0	–	—	0.10
Total carnitine level	44.8 ± 27.8	248.0 ± 190.0	113.8 ± 68.4	–	0.25
Free carnitine level	29.1 ± 20.2	209.2 ± 182.0	75.1 ± 51.4	–	0.03
N-terminal-pro-brain-natriuretic peptide	20,589 ± 21,841	7,310.5 ± 4,557.1	3,400 ± 3,339.1	1,544,0 ± 1,645.1	0.03
Troponin I	6.12 ± 12.65	1.29 ± 2.05	0.14 ± 0.07	0.02 ± 0.01	0.17
Blood urea nitrogen	16.1 ± 9.3	18.4 ± 10.0	18.4 ± 21.0	11.1 ± 4.7	0.17
Creatinine	0.51 ± 0.28	0.40 ± 0.31	0.37 ± 0.22	0.30 ± 0.19	< 0.01
Aspartate aminotransferase	150.7 ± 316.5	29.9 ± 22.7	55.2 ± 64.4	33.1 ± 9.0	0.37
Alanine aminotransferase	66.9 ± 149.0	33.2 ± 32.3	63.7 ± 104.3	28.1 ± 4.2	0.58
Lactate	3.6 ± 3.4	1.0 ± 0.4	–	–	< 0.01
Heart rate	139.3 ± 23.7	136.0 ± 26.2	135.4 ± 28.8	117.3 ± 16.5	0.42
Systolic blood pressure	83.5 ± 18.6	83.0 ± 16.1	85.9 ± 9.7	95.2 ± 10.4	0.72
Diastolic blood pressure	49.7 ± 15.9	50.4 ± 12.8	47.9 ± 7.5	56.0 ± 8.5	0.46
Cerebral near infrared spectroscopy	71.8 ± 10.4	76.0 ± 7.5	–	–	0.18
Renal near infrared spectroscopy	78.9 ± 10.1	78.3 ± 8.9	–	–	0.85

	Baseline	1-week after carnitine initiation	1-month after carnitine initiation	6-months after carnitine initiation	p-value
Vasoinotrope score	12.6 ± 4.5	3.5 ± 4.0	–	–	0.04

Echocardiographic changes after carnitine initiation

Table 6 summarizes the changes in echocardiographic indices at the various timepoints. LVEF significantly improved over the study period, increasing from 50.5–56.6% ($p < 0.01$). When ejection fraction was adjusted for other interventions (mechanical ventilation, afterload reduction, diuretic therapy, Spironolactone), the estimated means demonstrated a significant increase from 45.7–58.0% ($p < 0.01$).

Left ventricular shortening fraction did not demonstrate significant change, increasing from 28.5–29.8% over the study period ($p = 0.10$).

Left ventricular global longitudinal strain improved over the study period, increasing from − 9.3% to -17.2%, although did not reach statistical significance ($p = 0.10$).

	Baseline	1-week after carnitine initiation	1-month after carnitine initiation	6-months after carnitine initiation	p-value
Unadjusted LVEF (%)	50.5 ± 21.0	51.7 ± 16.6	52.8 ± 14.3	56.6 ± 10.3	< 0.01
Adjusted EVEF (%)*	45.7 ± 16.0	49.0 ± 2.6	49.9 ± 9.3	58.0 ± 7.4	0.04
*Adjusted for need for mechanical ventilation, afterload reduction, diuretic therapy, spironolactone therapy					

Table 6. LVEF before and after the adjustment for other interventions (mechanical ventilation, afterload reduction, diuretic therapy, Spironolactone)

Laboratory marker changes after Carnitine initiation

Free carnitine level significantly increased over the study period compared to baseline ($p = 0.03$). N-terminal-pro-brain-natriuretic peptide ($p = 0.03$), creatinine ($p < 0.01$), and lactate ($p < 0.01$) all significantly decreased over the study period (Table 5).

Hemodynamic changes after carnitine change

There was no statistical significance on heart rate or blood pressure (both systolic and diastolic) after carnitine supplementation ($p = 0.42$, 0.72, and 0.46 respectively).

There were no significant changes in near infrared spectroscopy values.

Regression analyses

The regression analysis was done to model ejection fraction with time point included as an independent variable demonstrated that time was not significantly associated with ejection fraction (beta-coefficient 1.52, p-value 0.08).

Paired regression analysis done to model change in ejection fraction from baseline to the 6-month time point demonstrated that a lower baseline ejection fraction was associated with a greater increase in ejection fraction. For every 1 lower the ejection fraction (%) at baseline there was 0.6 greater increase in the ejection fraction over the 6-month time period. The other independent variables were not found to be independently associated with the change in ejection fraction.

Discussion

This study demonstrated carnitine may be associated with an increase in LVEF in pediatric patients with left ventricular systolic dysfunction. Carnitine was also associated with improvement in markers of myocardial stress in N-terminal-pro-brain-natriuretic peptide, markers of aerobic metabolism in serum lactate, and markers of kidney function in creatinine over a 6-month study period. As LVEF was the primary focus of this study, these values were adjusted for other concomitant interventions and a significant increase remained. Adjusted LVEF increased from 45.7% immediately prior to carnitine initiation to 58.0%, representing an absolute increase of 12.3% in LVEF over 6-months.

Previous studies have demonstrated similar increases in LVEF. Pooled analyses by Loomba et al demonstrated that in 144 pediatric patients across six studies LVEF significantly increased by 3.68%. These same pooled analyses also demonstrated a significant increase in left ventricular shortening fraction [5].

The original studies included in the aforementioned pooled analyses included three with cardiomyopathy patients. Of these, only two, that by Wang et al as well as that by Kotby et al quantified ventricular function by ejection fraction, both noting improvements in ejection fraction and shortening fraction associated with carnitine. Both studies also demonstrated improvement in clinical symptoms associated with carnitine [6, 7]. Thus, this current study is among a small number of studies focusing on delineating the effect of carnitine supplementation on LVEF in children with left ventricular systolic dysfunction.

Cardiomyocytes rely on β-oxidation, the aerobic breakdown of fat within the mitochondria, to produce energy [6]. Levocarnitine, or L-carnitine, is a cofactor [8] involved in the transport of fatty acids across the inner mitochondrial membrane. L-carnitine plays an integral role in ATP production and assists in removing acylcarnitine derivatives from the mitochondria [9]. Defects in the carnitine shuttle can impair mitochondrial energy production. The myocardium cannot synthesize carnitine and thus relies on the liver and kidney as well as dietary sources to provide the necessary carnitine to transport fatty acids across the mitochondrial membrane. Neonates and infants in particular have decreased biosynthetic capacity and are at risk of developing carnitine deficiency, particularly when they are not receiving enteral nutrition [10, 11].

In the process of β-oxidation, the fatty acid is activated into fatty acyl-CoA by coenzyme A. The fatty acyl-CoA cannot cross the inner mitochondrial membrane without carnitine which acts as a cofactor. Carnitine acyltransferase I enables the formation of an acylcarnitine molecule which can be transported across the inner mitochondrial membrane by Carnitine acyltranslocase. In the mitochondrial matrix, carnitine acyltransferase II transfers the fatty acylcarnitine molecule back to CoA forming fatty acyl-CoA. The fatty acyl-CoA can then undergo β-oxidation [12].

Through the aforementioned process, carnitine modulates the transfer of fatty acids into the mitochondrial matrix. Once this transfer is complete, Carnitine can be relocated to the cytosol by carnitine acyltranslocase. Carnitine acyltransferase II may complex carnitine with acyl-CoA in the mitochondrial matrix to form an ester. The ester may be removed from the mitochondria by translocase providing a pathway to remove acyl derivatives [13].

Carnitine is an especially attractive option for intervention in this patient population as it has few adverse effects. Most adverse effects are gastrointestinal symptoms such as reflux and diarrhea [12]. Those with known seizure disorders may have increased frequency of seizures potentially related to carnitine and thus carnitine must be used with caution in this patient population [14].

In addition to its limited adverse event profile, carnitine is also fairly inexpensive. Using local data, carnitine is approximately $0.40 per 200 mg. Using the mean weight and mean daily dose from the current study results in approximately 1,000 mg/day of carnitine being prescribed. At the local price for carnitine that translates into a $2.00 daily cost of carnitine in the current study population. To put this in perspective, afterload reduction with enalapril in our population at 0.1mg/kg twice daily would result in about 3mg daily at a local of $4.30 per mg. This results in a total daily cost of $12.90 for enalapril in this population. Using the adjust means for LVEF, there was an absolute increase in ejection fraction of 4.2 over the 6-month study period. This would result in a $360 cost of carnitine in this period for the 4.2 increase noted in ejection fraction. Previous studies have demonstrated indirect association of LVEF and self-reported quality of life scores [15–17]. Thus, a 4.2 increase in ejection fraction associated with carnitine and its associated cost may also lead to meaningful increase in quality of life. This further highlights the potential cost effectiveness of carnitine in the setting of pediatric left ventricular systolic dysfunction.

This study is not without limitations. The most apparent limitation of this study is the lack of a control group in this retrospective study. This was not a controlled study with a non-carnitine arm. While the paired statistical analyses in this study utilize the patient's baseline levels as controls there remains the possibility that the ejection fraction would have improved with time without carnitine. While the effects of other medications can be estimated and adjusted for in these analyses as not all patients received them at any single point, this cannot be done for carnitine as inclusion into the study was based on receiving carnitine. Thus, time and carnitine are essentially combined as a variable in the paired regression analyses without the real ability to discern what degree of the change was from either component in the paired analyses. A regression analysis was conducted in an unpaired fashion to help determine the

independent association of time and ejection fraction and this demonstrated no significant association between time and ejection fraction. Another recently published pediatric study has also shown improvement in echocardiographic parameters with carnitine supplementation, perhaps further supporting the potential impact of carnitine on cardiac function [11].

Despite the limitations, these data are additive to the literature as they are able to quantify the effect of carnitine and the other medications over the same time-period even though the effect of time itself cannot be quantified. Additionally, the current study demonstrates safety of carnitine in pediatric patients with left ventricular dysfunction.

Conclusion

Carnitine supplementation in pediatric patients with left ventricular systolic dysfunction may be associated with increase in LVEF and improvement in laboratory markers of myocardial stress and cardiac output.

Declarations

Declarations of Interest: None

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