SJMS | E-ISSN: 2833-3772 | Volume 5 (2026), Issue 1 | Jan-Feb 2026

The Scientific Journal of Medical Scholar

Publisher and Owner: Real-Publishers Limited (Realpub LLC)

30 N Gould St Ste R, Sheridan, WY 82801, USA

Associate Publisher: The Scientific Society of Educational Services Development [SSESD], Egypt

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The Scientific Journal of Medical Scholar

Available on Journal Website
https:// https://sjms.realpub.org/index.php/sjms/index
Subject (Cardiothoracic Surgery)

Original Article

L-Carnitine for Children Undergoing Open Cardiac Surgery for Congenital Heart Disease: A retrospective Study

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Article information: Received: October 8th, 2025; Accepted: January 30th, 2025; DOI: 10.55675/scijmedscholar.v5i1.16

Citation: Elnahhas MAZ, Mahmoud AS, Tantawy AMG, Shaien AGM, Elmetwaly MAM. L-Carnitine for Children Undergoing Open Cardiac Surgery for Congenital Heart Disease: A retrospective Study. SJMS 2026 Jan- Feb; 5 (1): 48-53. DOI: 10.55675/scijmedscholar.v5i1.16

ABSTRACT

Background: Cardiac surgery in pediatrics is associated with myocardial injury with potential increase of morbidity and mortality. Methods to protect against this injury are of crucial importance. L-carnitine seems to have a potential protective effects. However, this needs further confirmation and elucidation of possible mechanisms. This study was designed to investigate the potential protective effects of L-carnitine on the cardiac injury after open heart surgery in pediatrics.

Patients and Methods: This was a multicenter retrospective study. It included 100 children, age 2-5 years, divided into two equal groups. The first group included 50 children who received L-carnitine 50 mg/kg/day in a single daily dose for at least two weeks before cardiac surgery. The second group included 50 children matched for age and sex with the study group who were not used L-carnitine before surgery. The collected data include patient demographics, type of congenital heart defect, laboratory data (indicators of cardiac injury, oxidative stress markers and apoptosis marker caspase-3). Laboratory workup was repeated at the end of the first postoperative day. Operative data and postoperative morbidity and in-hospital mortality were recorded.

Results: Both study and control groups were comparable regarding patient demographics and preoperative data. Males represented 56% and 60.0% of study and control groups, respectively. Atrial septal defect (ASD) and ventricular septal defect (VSD) were reported in 40% and 60% respectively with no significant differences between groups. Postoperatively, cardiac Troponin-I, CK-MB, MDA, and Caspase-3 were significantly lower in study than control groups (0.52±0.089, 26.22±3.84, and 0.43±0.037 vs 1.62±0.38, 41.46±5.71 and 5.49±0.25, successively). However, SOD, and left ventricle EF% were significantly higher in the study than in the control group (3.86±0.47 and 62.06±1.89 vs 3.17±0.33 and 56.82±1.22, respectively). The need for inotropic drugs, development of arrhythmias was lower in the study then the control group. But the difference did not reach statistical significance. No in-hospital mortality was recorded. In control group, ejection fraction was significantly reduced after than before surgery (56.82±1.22 vs 62.20±2.59 respectively). However, in study group, this difference was non-significant.

Conclusion: Preoperative administration of L-carnitine for at least 2 weeks before open heart surgery was associated with a potential protective effect against cardiac injury induced by surgery in pediatrics.

Keywords: Cardiomyocytes; Oxidative Stress; Ventricular Septal Defect; Atrial Septal Defect; Apoptosis; L-carnitine.

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INTRODUCTION

Cardiac surgery for congenital heart disease is associated with a myocardial injury and dysfunction which was associated with postoperative morbidity and mortality. The possible mechanisms include ischemia–reperfusion injury after removal of the aortic clamp, production of reactive oxygen species (ROS) and liberation of inflammatory mediators [1-4].

The pediatric heart (especially in early years of life) had an immature antioxidant defenses. Thus, it is more susceptible to harmful effects of oxidative stress. Liberation of reactive oxygen species stimulates myocardial injury through different mechanism (for example lipid peroxidation, changes in proteins, or induction of cardiomyocyte apoptosis) [5-8].

Interestingly, apoptosis is associated with an activation of caspases. Of these, capase-3 play a crucial role in the process of apoptosis and usually used as a marker of apoptosis after cardiac surgery [9-11].

Song *et al.* [12] conducted meta-analysis to investigate the potential benefits of L-carnitine for patients with chronic heart failure (CHF). They concluded that L-carnitine treatment is effective for CHF patients in improving clinical symptoms and cardiac functions. In addition, it reduced serum levels of brain natriuretic peptide (BNP), with good tolerance.

After that, **Cruz *et al.*** [13] reported that supplementation by L-carnitine at a daily oral dose of 50 mg/kg in patients with heart failure undergoing coronary artery bypass grafting (CABG) may recover preoperative plasma L-carnitine within 10 days.

Sato *et al.* [14] reported that, L-carnitine can potentially alleviate chronic fatigue in patients with liver cirrhosis through antioxidant mechanisms. In addition, serum carnitine concentrations were positively correlated with changes in serum albumin levels. Furthermore, total mental and physical scores were improved significantly 3 and 6 months after initiation of L-carnitine supplementation.

Most recently, **Shalabi *et al.*** [15] conducted a systematic review and meta-analysis to investigate the effect of preoperative administration of L-carnitine before cardiac surgery. Results showed that, L-carnitine provides a significant short-term benefit, as it increased cardiac index (CI), left ventricular stroke work index (LVSWI) and left ventricular ejection fraction (LVEF). In addition, it reduced postoperative atrial fibrillation (POAF) after cardiac surgery. They concluded that L- carnitine supplementation enhanced recovery and decreased postoperative complications after cardiac surgery. However, the existing studies are limited in scope. Thus, conclusions must be treated carefully.

Based on the previous evidence, we hypothesized that, L-carnitine supplementation before cardiac surgery for congenital heart disease may reduce cardiac injury associated with open heart surgery. To investigate this hypothesis, we performed this retrospective study to elicit evidence about potential benefits of L-carnitine supplementation before open cardiac surgery in pediatrics.

PATIENTS AND METHODS

Study design and settings: This was a multicenter retrospective study. The data was collected from patients attending cardiothoracic surgery of the following hospital (Nasser Institute Hospital and Al-Azhar University Hospitals).

We were able to collect data for 100 children, who were divided into two equal groups according to the state of preoperative L-carnitine supplementation.

The first group (Study group) included 50 children younger than 6 years of age, who received L-carnitine 50 mg/kg/day in a single daily dose for at least two weeks before cardiac surgery. The second group (Control group) included 50 children matched for age and sex with the study group, who were not used L-carnitine before surgery.

We collected data of children aged 2 to 5 years of age who were submitted to open heart surgery for congenital heart disease (atrial septal defect or ventricular septal defect). However, we excluded data of children who had heart failure, infective endocarditis, liver or renal disease, metabolic diseases or who used anti-inflammatory or antioxidant drugs in the last month before surgery.

Ethical aspects:

Required administration consents were obtained from the corresponding facility (hospital) administration manager. But, patient consent had been not required. However, collected data were coded to assure patient anonymity and data were used for the purpose of research only.

The available data of cardiac function was the left ventricular ejection fraction, which was measured before administration of L-carnitine (study group) and at the end of the first postoperative data using conventional echocardiography. In control group, two measures were also recorded, at admission, which compared to basal measurement in L-carnitine group and at the same time postoperatively as in the study group.

At the same time of echocardiography, a venous blood sample was drawn for different laboratory workup. The available laboratory data included the following:

1) **Cardiac Troponin-I and serum creatine kinase-MB** (CK-MB);

2) **Serum malondialdehyde** (MDA) and superoxide dismutase (SOD) activity (as oxidative stress markers). SOD is an enzyme working to catalase superoxide radicals into molecular oxygen and hydrogen peroxide. However, MDA is a marker of lipid peroxidation and reflected the oxidative stress status;

3) **Caspase-3 as** a marker of cardiomyocyte apoptosis.

In addition, aortic clamp duration (minutes) and cardio-pulmonary bypass times (minutes) were recorded and compared between groups.

Postoperative, besides the laboratory data, the need for inotropes, episodes of arrhythmias and in-hospital mortality were recorded.

Statistical analysis:

Collected data were coded and fed to personal computer for analysis using statistical package for social sciences (SPSS version 22) (IBM Inc., USA). Continuous quantitative variables were expressed by their mean, standard deviation (SD) and sometimes the minimum and maximum values, regardless of data normality of distribution.

On the other side, categorical variables were summarized by the frequency (numbers) and relative percentages. Study and control groups were compared by the independent student samples "t" test and Chi square test for quantitative categorical variables, respectively.

In each group, basal and postoperative values were compared using paired samples t-test. The p value < 0.05 was considered significant from the statistical point of view.

RESULTS

In the current work, we are able to collect data for 100 children with congenital heart disease who were submitted to Open Cardiac Surgery during the last years (2022-2025). They were divided into two equal groups according to administration of L-carnitine before surgery.

The first group which received L-carnitine was assigned as a study group and the other was the control group.

The patient age ranged between 2 and 5 years with slight male sex predominance (males represented 56% and 60.0% of study and control groups, respectively).

The congenital heart diseases were in the form of atrial septal defect (ASD) (40.0%) and ventricular septal defect (VSD) (60.0%), with normal ejection fraction in both groups (all were above 55%).

There were no significant differences between study and control groups regarding patient demographic or cardiac and oxidative stress biomarkers.

Finally, the aortic clamp duration ranged between 28 and 40 minutes, while cardiopulmonary bypass time ranged between 45 to 62 minutes.

Again there was no significant differences between study and control groups **(detailed results in table 1).**

Postoperatively, cardiac Troponin-I, CK-MB, MDA, and Caspase-3 were significantly lower in study than control groups (0.52 ± 0.089, 26.22 ± 3.84, and 0.43 ± 0.037 vs 1.62 ± 0.38, 41.46 ± 5.71 and 5.49 ± 0.25, successively). However, SOD, and left ventricle EF% were significantly higher in the study than in the control group (3.86 ± 0.47 and 62.06 ± 1.89 vs 3.17 ± 0.33 and 56.82 ± 1.22, respectively).

Furthermore, the need for inotropic drugs, development of arrhythmias was lower in the study then the control group. But the difference did not reach statistical significance. No in-hospital mortality was recorded in any of groups **(Table 2).**

In the study group, postoperative values of Troponin-I, CK-MB, MDA, SOD and Caspase-3 were significantly different after surgery than preoperative values. However, left ventricular ejection fraction showed non-statistical differences. All were increased, except SOD which was reduced.

In the control group however, all postoperative values were significantly different than preoperative corresponding values including ejection fraction, which was significantly reduced after than before surgery (56.82 ± 1.22 vs 62.20 ± 2.59 respectively) **(Table 3).**

Table (1): Comparison between study and control groups as regards preoperative data

Variable	*Measures*	*Study (n=50)*	*Control (n=50)*	*Test*	*p*
Age (year)	Mean±SD	3.60±1.01	3.70±0.84	0.539	0.591
	Min. – Max.	2-5	2-5		
Sex (n,%)	Male	28(56.0%)	30(60.0%)	0.164	0.685
	Female	22 (44.0%)	20 (44.0%)		
Anomaly	ASD	17 (34.0%)	23 (46.0%)	1.50	0.221
	VSD	33 (66.0%)	27 (54.0%)		
Ejection Fraction %	Mean±SD	61.80±2.45	62.20±2.58	0.792	0.430
	Min. – Max.	57-66	58-68		
CK-MB (U/L)	Mean±SD	5.45±0.37	5.61±0.50	1.801	0.075
	Min. – Max.	4.9 – 6.3	4.5-6.9		
Troponin-I (ng/L)	Mean±SD	0.129±0.028	0.123±0.015	1.397	0.165
	Min. – Max.	0.08 – 0.20	0.10- 0.15		
MDA (nmol/ml)	Mean±SD	3.65±0.55	3.87±0.82	1.52	0.123
	Min. – Max.	2.80- 5.10	2.8- 7.2		
SOD (U/L)	Mean±SD	4.47±0.69	4.32±0.82	1.01	0.316
	Min. – Max.	2.8- 6.0	2.8- 7.2		
Caspase-3 (ng/ml)	Mean±SD	0.31±0.029	0.32±0.036	0.845	0.400
	Min. – Max.	0.25- 0.36	0.22- 0.42		
Aortic Clamp Duration (min)	Mean±SD	33.86±2.42	34.26±1.61	0.974	0.333
	Min. – Max.	28-40	29-36		
Cardiopulmonary bypass time (min)	Mean±SD	51.50±2.19	52.38±3.42	1.535	0.128
	Min. – Max.	45-60	46-62		

Table (2): Comparison between study and control groups as regards postoperative data

	Study (n=50)		Control (n=50)		Statistics	
	Mean	S. D	Mean	S. D	Test	P value
Troponin-I (ng/L)	0.52	0.089	1.62	0.38	19.63	<0.001*
CK-MB (U/L)	26.22	3.84	41.46	5.71	15.65	<0.001*
MDA	4.32	0.59	5.30	0.37	10.06	<0.001*
SOD	3.86	0.47	3.17	0.33	8.39	<0.001*
Caspase -3	0.43	0.037	5.49	0.25	139.6	<0.001*
LVEF%	62.06	1.89	56.82	1.22	16.46	<0.001*
Inotropic needs	4 (8.0%)		9 (18.0%)		2.21	0.137
Arrhythmias	2 (4.0%)		4 (8.0%)		0.709	0.400
In-hospital mortality	0 (0.0%)		0 (0.0%)		-	-

Table (3): Comparison between pre and post-operative data in each group

		Preoperative		Postoperative		Statistics	
		Mean	S. D	Mean	S. D	Paired (t)	P value
Study group	Troponin-I (ng/L)	0.129	0.028	0.52	0.089	28.67	<0.001*
	CK-MB (U/L)	5.45	0.37	26.22	3.84	37.98	<0.001*
	MDA	3.65	0.55	4.32	0.59	6.17	<0.001*
	SOD	4.47	0.685	3.86	0.47	5.15	<0.001*
	Caspase -3	0.317	0.030	0.43	0.037	17.81	<0.001*
	LVEF%	61.80	2.46	62.06	1.89	0.63	0.529
Control group	Troponin-I (ng/L)	0.123	0.015	1.62	0.38	27.57	<0.001*
	CK-MB (U/L)	5.61	0.50	41.46	5.71	44.01	<0.001*
	MDA	3.87	0.82	5.30	0.37	10.85	<0.001*
	SOD	4.32	0.82	3.17	0.33	9.29	<0.001*
	Caspase -3	0.32	0.036	5.49	0.25	139.32	<0.001*
	LVEF%	62.20	2.59	56.82	1.22	12.99	<0.001*

DISCUSSION

Preoperative supplementation by L-carnitine for at least 2 weeks was associated with a significant reduction of cardiac enzymes (Troponin-I and CK-MB) when compared to control group. In addition, results showed a significant reduction of post-operative apoptotic markers (caspase-3), oxidative stress markers (significant reduction of MDA and significant increase of SOD). These results reflected the potential ameliorative effect or cardiac damage of L-carnitine in the open cardiac surgery for congenital heart diseases in pediatric patients. These potential protective effective can be attributed to antioxidant and anti-apoptosis mechanism, among others.

In the current work, Troponin I and CK-MB were significantly reduced in the study than the control groups after sugary. However, both were comparable before surgery and in each group, Troponin I and CK-MB were significantly increased after than before surgery. This reflected the cardiac injury associated with open heart surgery, which was ameliorated with preoperative L-Carnitine. These results are comparable to previous literature, where troponin I and CK-MB are the most important diagnostic indicators for myocardial injury, which was significantly increased after open-heart surgery in pediatrics as well as adults [16-19].

In the current work, postoperative ejection fraction was significantly increased in the study than the control group reflecting the potential protective effects of L-carnitine with improvement of left ventricle cardiac function. These results are consistent with previous literature [20,21].

Juricic *et al.* [22], **El Feky *et al.*** [23] **and Fischer *et al.*** [24] reported that, cardiomyocyte apoptosis (programmed cell death) are increased after open heart surgery by different mechanisms (for example, increased oxidative stress, increased production of cytokines and stretched myocardium). Oxidative stress was attributed to cardioplegia with ischemia reperfusion injury of myocardium. These results are supported by the current study.

In addition, our results revealed significant increase of postoperative apoptosis marker caspase-3 in both study and control groups when compared to preoperative values. However, values in study group were significantly lower than the control group. These results confirmed the myocardial injury induced by open heart surgery and potential ameliorative effects of L-carnitine. These results are in line with **El Feky *et al.*** [23] **and Kim M, *et al.*** [25].

Our results are also consistent with that of **Li M, *et al.*** [26] and **Xiang *et al.*** [21] who reported that, preoperative administration of L-carnitine exerts a protective effect against myocardial injury associated with cardiopulmonary bypass. This was exerted by reduced cardiomyocyte apoptosis among other mechanism. These mechanisms my included stabilization of mitochondrial membrane of cardiac cells, reduced mitochondrial release of Cytochrome-C and inhibition of caspase cleavage and activation, reducing levels of Bax expression, increasing levels of phosphorylation of Akt, PI3K, and Bcl-2 protein expression [27,28].

The antioxidant effects of L-carnitine as evidenced by significant reduction of postoperative MDA and significant increase of postoperative SOD in the study than the control group. This antioxidant effects may be due to the ability of L-carnitine to activate nuclear factor erythroid 2-related factor 2 (Nrf2); the transcription factor regulating the expression of antioxidant enzymes, attenuation of the Na/K-ATPase/Src/ROS amplification signaling pathway, and its ability to decrease the production of ROS [26,29].

In conclusion, preoperative administration of L-carnitine for at least 2 weeks was associated with a protective effect against cardiac injury induced by open heart surgery in pediatrics. The current work had the strength of being a multicenter study. However, it is limited by retrospective nature (Increased liability to bias). Thus, future prospective large scale studies are warranted.

Financial and non-financial relationships and Activities of Interest: None

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SJMS | E-ISSN: 2833-3772 | Volume 5 (2026), Issue 1 | Jan-Feb 2026

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