ORIGINAL ARTICLE

Effect of Carnitine in Diphtheria - A Preliminary Report)*

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ABSTRACT A double blind, placebo controlled trial was conducted on 68 diphtheria patients who were hospitalized in pediatric ward of Kariadi Hospital, Semarang, from 1 April 1990 to 31 March 1991. The age range of the patients was between 7 months to 13 years, with the median of 48 months and the mean of 60.5 (SD11) months. The pre-treatment characteristics of both groups were similar with respect to sex, the clinical condition on admission, presence of bullneck, nutritional and immunization status. Oral carnitine was administered with a dose of 100 mg/kg/day divided into 3 doses. Other standard treatment was administered to all patients. Post-treatment comparisons were performed on the prevalence of myocarditis, CK-MB level examined on the fifth day of treatment, and mortality. It was found that the prevalence of myocarditis and CK-MB levels were significantly less than those in the placebo group, while the mortality in the carnitine group (3%) although smaller than in placebo group (17%) was not statistically different. It seems that l-carnitine is useful to prevent diphtheritic myocarditis, while its effect on improving the overall prognosis needs further study. **[Paediatr Indones 1999; 39:102-107]**

Introduction

Diphtheria is an acute infection characterized by low grade fever and the presence of pseudomembrane which is difficult to remove and is easily bleeding on the tonsil, pharynx, palatum and tongue. This disease is attributed to a very infectious *Corynebacterium diphtheriae*. Diphtheria complication is basically due to the widening of membrane and due to the diphtheria toxin.[1,2] Diphtheria toxin can damage almost all systems and has selective affinity against the muscular and nervous system. Diphtheria toxin decreases fatty acid oxidation by affecting carnitine metabolism.

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Carnitine is a co-factor which enables the fatty acid transportation from extramitochondrial cytoplasm, into the mitochondria where the fatty acid is being oxidized. In diphtheritic myocarditis there is carnitine depletion in the cardiac muscle cell. The objective of this study was to determine whether diphtheritic myocarditis prevalence can be decreased by administering carnitine.

Methods

This was a double blind randomized controlled trial to determine the effects of carnitine in the clinical course and prognosis of patients with diphtheria. Subjects were recruited consecutively on the diphtheria patients hospitalized in the pediatric ward of Dr. Kariadi Hospital, Semarang, from 1 April 1990 to 31 March 1991. Patients with congestive heart failure, cardiogenic shock, and diphtheritic laryngitis with signs of obstructive respiratory tract were not included in this study.

The patients were randomly allocated into two groups either to receive carnitine or placebo besides standard treatment. Carnitine is administered in the form of oral, syrup with the dose of 100 mg per kg of body weight per day, divided into 3 doses, during the period of treatment in the hospital. Standard medications were administered, namely crystalline procaine penicillin and diphtheria antitoxin according to the standard dose. Clinical conditions at the time of arrival (bullneck or non-bullneck), membrane location, nutritional status, immunization status as well as age and sex were recorded for further analysis.

On the fifth day of treatment, serum CK-MB content and electrocardiography (ECG) were examined. Myocarditis was diagnosed by ECG in the form of prolonged PR interval and depressed ST segment, widened QRS complex, along with CK-MB level of more than 10 U/L, or the occurrence of intraventricular block or other major conduction blocks.

Results

From 1 April 1990 to 31 March 1991, 68 patients were enrolled in the study. They were divided into two groups, i.e. 34 patients of carnitine group and 34 patients of placebo group. Their age ranged from 7 months to 13 years with the median of 48 months and average 60.5 (SD 11) months. Most patients were of 1-5 years (52%) age group, followed by 5-10 years (31%) age group (Table 1). Tables 2 shows that subjects in both groups were not different with respect to sex, proportion of bullneck, membrane location, and nutritional and immunization status.

There were less patients in carnitine group who had CK-MB content of more than 10 U/L than those of the control group (4 versus 7). Statistically it shows significant

difference (p = 0.001, Table 3). It is also shown in Table 4, that the occurrence of myocarditis based on ECG examination in carnitine group was less than that in placebo group (3 versus 13), and the difference was statistically significant. The mortality rate of the two groups, however, was not significantly different, although in the carnitine group there were less patients who died (Table 5). Regarding the hospital stay, the mean duration of hospitalization in carnitine group was 8 days, while in placebo group it was 8.8 days.

Table 1. Age distribution in the two groups

Age (yr)	Carnitine group	Placebo proup	Total
0-1	3	5	8
1-5	17	18	35
5-10	12	9	21
>10	2	2	4
Total	34	34	68

Table 2. Clinical characteristics of patients in carnitine and placebo groups

	Carnitine group n = 34	Placebo group n = 34	p
Sex			
▪ Male/Female	22/12	23/11	0.798
Bull-Neck			
▪ Yes/No	11/23	8/26	0.417
Diagnosis			
▪ Tonsilitis	28	27	0.947
▪ Faucial	5	6	
▪ Laryngitis	1	1	
Nutrition			
▪ Good/Malnourished	20/14	17/17	0.465
Immunization			
▪ Complete/Incomplete	14/20	13/21	0.804

Table 3. Comparison of CK-MB content of the two groups

CKMB	Carnitine Group	Placebo Group	Total
≥10	30	17	47
<10	4	17	21
Total	34	34	68

p=0.001

Table 4. Comparison of the occurrence of myocarditis in the two groups

	Myocarditis		
Treatment Group	Yes	No	Total
Carnitine	3	31	34
Placebo	13	21	34
Total	16	52	68

p=0.004

Table 5. Outcome of the two groups

Group	Survived	Died	Total
Carnitine	33	1	34
Placebo	29	5	34
Total	62	6	68

p=0.087

Discussion

Diphtheria toxin affects the cardiac muscle at least in 2 ways, namely, affecting the fat metabolism and obstructing the protein synthesis. In heart which is metabolically mature, glucose, lactate and fatty acid are used alternately as a substrate to obtain energy. Free fatty acid fulfills 60-70 percent of the energy required by the cardiac muscle, while glucose is responsible of more or less 30 percent of the requirement.[4,6]

Study have shown that diphtheria toxin decreases fatty acid oxidation by affecting carnitine metabolism.[3] Carnitine is a co-factor which enables the transportation of

fatty acid from cytoplasm extra-mitochondrial cytoplasm into the mitochondria, where the fatty acid is oxidized (Figure 1). The block in protein synthesis due to diphtheria toxin decreases the mount of carnitine in the cardiac muscle. This is proved by fact that carnitine depletion in the cardiac muscle cell is the specific character which happens on diphtheritic myocarditis.[3,5,6]

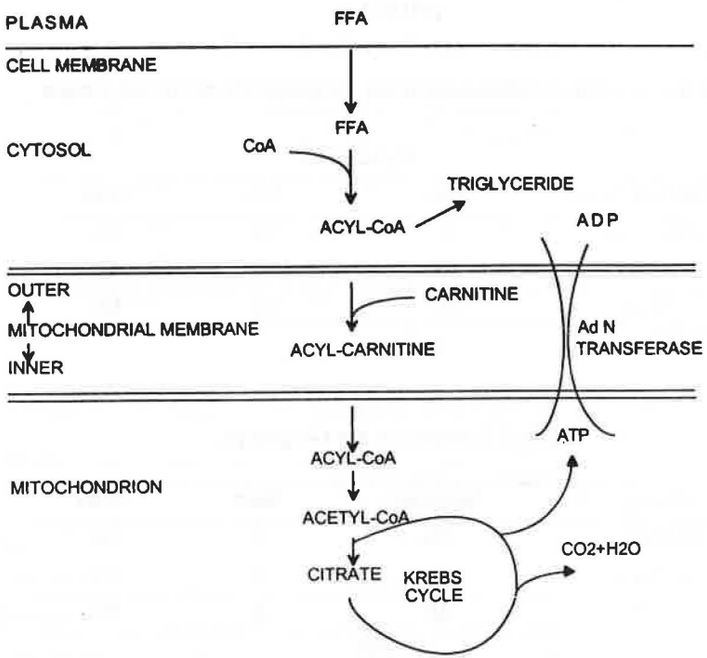

Fig 1. Pathway of fatty acid metabolism. (FFA = free fatty acid; CoA = coenzyme A, ADP = adenosine diphosphate

In 1971 Challoner et al[5] gave exogenous l-carnitine to experimental animal with diphtheritic myocarditis. It turned out that it decreased the mortality rate and improved the cardiovascular function of the animal having cardiovascular depression.[5]

Then Ramos et al[4] conducted a control study by giving carnitine 100 mg per kg of body weight per day for four days to 132 patients with diphtheria. On the carnitine group it was found that the myocarditis prevalence was less, there were less congestive heart failure, less digitalis and diuretic requirement, less cases with patients who

need temporary cardiac pace maker on major conduction block, which all of them statistically significant compared to the control group.

In this study, there have been 34 patients with diphtheria who are treated with carnitine and work out well in decreasing the myocarditis diphtheria prevalence, which statistically shows significant difference compared with the placebo group. This gives us hope and encourage us to conduct more study with more specific variables so that in the end the carnitine can be used more widely.

To sum up, we have conducted a randomized double blind study to determine the benefit of carnitine treatment in diphtheria. It shows that carnitine administration is associated with the decrease in myocarditis but does not seem to significantly improve the overall prognosis. Further studies using more subjects are needed to understand the use of carnitine more widely.

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