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Original Article

Evaluation of Serum Carnitine Levels for Pediatric Patients Receiving Carnitine-Free and Carnitine-Supplemented Parenteral Nutrition

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Abstract

Purpose: Carnitine is a carrier molecule transporting long-chain fatty acids (LCFAs) into the mitochondria for fatty acid β-oxidation. The purpose of this study is to evaluate the role of carnitine supplementation in parenteral nutrition (PN) within the pediatric population. Our goal was to determine a weight range for which empiric carnitine supplementation is justified and to determine a weight range at which a carnitine level should first be drawn to confirm a deficiency prior to supplementation. Secondarily, we tried to determine a relationship among carnitine deficiency, hypoglycemia, and hypertriglyceridemia.

Methods: This was a retrospective observational study to evaluate 2 groups of pediatric patients (weighing 0.68 kg to 60 kg) who were NPO and receiving PN. The first group of patients (n = 454) received carnitine supplementation (15 mg/kg/day) upon initiation of PN. The second group (n = 299) did not receive carnitine supplementation until they were determined to have a carnitine deficiency.

Results: The data indicated that 82% of the patients weighing less than 5 kg were deficient. Patients weighing more than 5 kg had serum carnitine levels within the normal range. Therefore, patients receiving PN and weighing less than 5 kg should be supplemented with carnitine. Comparison of triglyceride, glucose, and carnitine showed no statistically significant difference (P = .1936).

Conclusion: Patients weighing more than 5 kg should have serum carnitine levels drawn within 7 days to determine whether supplementation is needed. There is no statistical correlation among carnitine deficiency, hypoglycemia, and hypertriglyceridemia.

Key Words—carnitine supplementation, infants, neonates, parenteral nutrition, TPN

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Carnitine is a nutrient that is made from the amino acids methionine and lysine.[1] Its primary role is to allow the transport of long-chain fatty acids (LCFAs) into the mitochondrial matrix for β-oxidation and energy production.[2] Additionally, carnitine assists with the oxidation of medium-chain fatty acids (MCFAs), freeing up CoA for the use in β-oxidation. This helps protect and repair oxidatively damaged cells.[3]

Carnitine is available exogenously, through meat and dairy products, as well as endogenously via synthesis by the liver and kidneys. Generally carnitine is produced in adequate quantities; however, certain populations may need to obtain additional carnitine from exogenous sources. Populations at increased risk of carnitine deficiency without exogenous supplementation include patients with metabolic disorders, renal insufficiency, liver insufficiency, increased urinary

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loss of carnitine, hemodialysis, patients taking medications including valproic acid and zidovudine, patients on prolonged PN, and neonates and infants.[3]

Carnitine has been considered a conditional essential nutrient in pediatrics.[4,5] It is initially transferred to the fetus during the third trimester of a pregnancy. Once the child is born, carnitine is typically obtained from the mother's breast milk or infant formula. However, if the child is not able to take food by mouth and receives total PN without carnitine supplementation, he or she is likely to deplete their carnitine stores.

Neonates and infants are generally unable to synthesize enough carnitine on their own due to their immature liver and kidneys. To biosynthesize carnitine, there must be adequate supplies of cofactors including ascorbic acid, iron, niacin, and pyridoxine.[3] The final step of carnitine biosynthesis requires γ-butyrobetaine hydroxylase. The pediatric population has about only 12% of this enzyme compared to adults.[3] As a result, some infants are not able to synthesize enough carnitine.

Carnitine is stored in the skeletal muscle, heart, liver, brain, and kidney and within plasma.[4] Carnitine is also found in the body in several different forms. Because of this, it can be difficult to assess a carnitine deficiency. Studies have defined carnitine deficiency as a free plasma carnitine concentration of less than 20 nmol/mL. An insufficiency is defined as an acylcarnitine to free carnitine ratio of greater than 0.4.[1]

A carnitine deficiency or insufficiency is based on the combination of decreased carnitine laboratory values and clinical symptoms. Depending on the severity of the deficiency, the infant may present with myopathies, limb weakness, hypotonia, hypoglycemia, hyperbilirubinemia, hypoketonemia, encephalopathy, coma, or even death.[2,3,4,6]

Studies have assessed the benefits of carnitine supplementation in infants and neonates. Most of these studies have looked at the very-low-birth-weight infants on PN and/or enteral feeds. The results have been inconsistent on carnitine supplementation in regard to weight gain and morbidity markers including episodes of apnea. None of these studies have had large sample sizes or been consistent in the method of carnitine supplementation. Additionally, none have evaluated different patient weight ranges in which supplementation should be empirically started versus when a carnitine level should be drawn. Two systematic reviews have been published and both concluded that there is not enough evidence to support routine supplementation of parenterally fed neonates despite the majority of studies showing a beneficial effect.[3] One article identified, in a small population of pediatric patients, that patients who received PN without supplemented carnitine had low serum carnitine levels.[7]

At Primary Children's Hospital, the amount of carnitine supplementation in PN increased more than 9-fold in 2012. This was in response to testing of carnitine levels in the neonate and infant population. In this study, we evaluated serum carnitine levels in patients to determine whether there was a weight range–specific deficiency and a statistical association for carnitine-supplemented patients versus non-supplemented patients. We assessed carnitine serum levels to determine whether there is a weight range at which carnitine should automatically be supplemented in PN without needing to draw a carnitine level. Additionally, we wanted to determine whether decreased glucose and elevated triglyceride levels are associated with a carnitine deficiency.

METHODS

This was a retrospective observational study approved by the institutional review board to evaluate 2 groups of pediatric patients (from 0.68 kg to 60 kg) who were NPO and receiving PN. The first group of patients (n = 454) received carnitine supplementation (15 mg/kg/day) upon initiation of PN. The second group (n = 299) did not receive carnitine supplementation until it was determined that they had a carnitine deficiency by a carnitine serum assessment. Standard laboratory carnitine values were assessed using total carnitine, free carnitine, esterified carnitine, and the ratio of esterified to free (**Table 1**). Carnitine deficiency was determined by low free carnitine levels or an esterified to free carnitine ratio greater than 0.4. Patients were assessed by weight ranges: 0 to 2.5 kg, 2.51 to 5 kg, 5.01 to 7.5 kg, 7.51 to 10 kg, and greater than 10 and less than 60 kg. Weight ranges were assessed to determine which weights had low levels of free carnitine requiring supplementation. Patients were excluded if they had cardiopulmonary bypass, extracorporeal membrane oxygenation

Table 1. Normal carnitine levels

Serum carnitine	Level
Total carnitine	34-86 μmol/L
Free	25-60 μmol/L
Esterified	5-29 μmol/L
Ratio	0.25-0.4

(ECMO), renal dialysis, or spinal muscular atrophy (SMA).

The free carnitine levels indicated that supplemented and nonsupplemented patients in the 0 to 5 kg and greater than 5 kg weight ranges could be compared by calculating the percentage of patients that were low, within normal limits (WNL), and high levels. A statistical review of supplemented and nonsupplemented carnitine-free levels was assessed using a Mann-Whitney nonparametric statistical test to determine whether there was a statistical difference in the supplemented versus nonsupplemented patients.

Triglyceride and blood glucose levels were evaluated in the nonsupplemented patients before and after carnitine supplementation if needed. Patients supplemented with carnitine initially had their triglyceride and blood glucose levels evaluated at the initiation of PN and 30 days later. A Mann-Whitney test was used to statistically evaluate the triglyceride and blood glucose levels in nonsupplemented and supplemented patients before and after PN.

RESULTS

Carnitine-supplemented patients (n = 454) received a dose of 15 mg/kg/day and averaged 30 days of supplementation before levels were obtained. In all weight ranges, the average total carnitine level, esterified carnitine level, and free carnitine level were found to be within the normal level range. The esterified to free carnitine ratio for the 0 to 2.5 kg and the greater than 10 kg patients were within the normal range of 0.25 to 0.4. However, the esterified to free carnitine ratio was high (average, 0.54) for the 2.51 to 5 kg, 5.01 to 7.5 kg, and 7.51 to 10 kg groups. The percentage of carnitine levels that were low, high, and within normal range can be seen in **Figure 1**.

In the nonsupplemented patients (n = 299), the number of days before a carnitine level was obtained averaged 13 days. Patients who had a low serum carnitine-free level were then dosed at 15 mg/kg/day. The average serum carnitine-free level for patients weighing 0 to 2.5 kg and 2.51 to 5 kg was low (17.64; range, 29–61) indicating a carnitine deficiency and thus requiring supplementation. The average serum carnitine-free levels for patients weighing 5.01 kg to 60 kg were within normal limits. The average levels for the total and esterified were abnormal for patients weighing 0 to 5 kg but were within normal limits for patients weighing more than 5.01 kg. The percentage of carnitine levels that were low, high, and within normal range can be seen in **Figure 1**. Using the Mann-Whitney test to compare the total

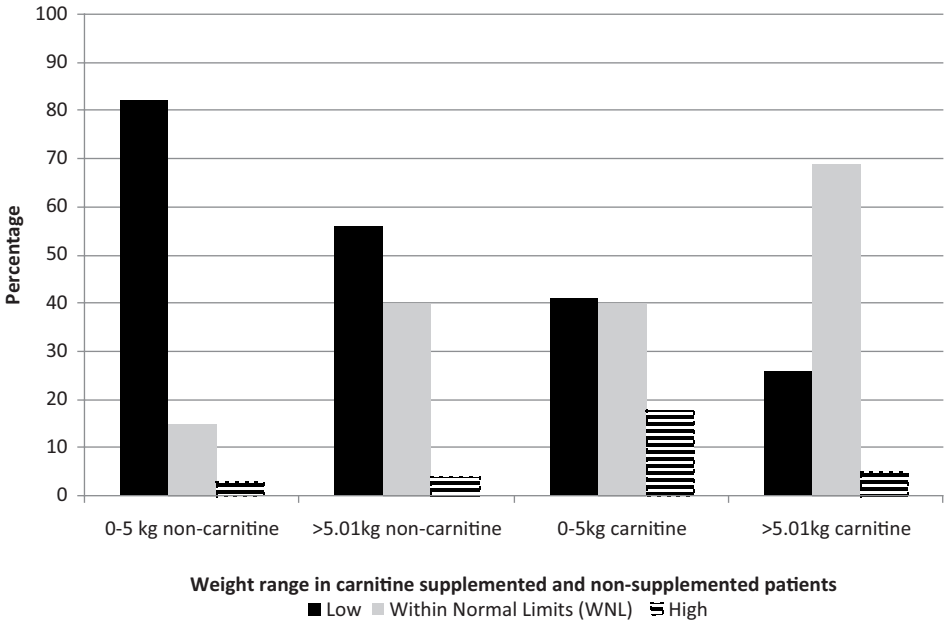

Figure 1. Percentage of total serum carnitine levels that are low, within normal limits, and high by weight in carnitine supplemented and nonsupplemented patients.

serum carnitine levels for the nonsupplemented and the supplemented patients, we found a difference (P = .001) (**Figure 2**).

A subset of 109 nonsupplemented patients was used to compare triglyceride and blood glucose levels before and after carnitine supplementation. The difference in the triglyceride levels before and after supplementation was not significant (P = .6965). Comparison of glucose levels before and after supplementation showed a lower glucose level after carnitine supplementation (P = .0414). We expected that low glucose levels with a carnitine deficiency reflected increased utilization of glucose due to decreased ability to utilize fat for energy, but our results did not support this. Using a ratio of the triglyceride level before and after supplementation and comparing the same ratio for the glucose level before and after supplementation showed no difference (P = .118).

In a subset of 54 carnitine-supplemented patients, the triglyceride and blood glucose levels were drawn at the initiation of carnitine supplementation and 30 days after supplementation. Comparing the triglyceride and blood glucose levels at the initiation of carnitine supplementation and 30 days after supplementation were not significant (P = .2983 and P = .131, respectively). Using a ratio of the triglyceride level before and after supplementation and comparing the same ratio for the glucose level before and after supplementation showed no difference (P = .1936).

DISCUSSION

This retrospective study was conducted because most research has been focused on patients weighing less than 2 kg. We found that patients need carnitine supplementation at a higher weight. The majority of our patients weighing less than 5 kg required supplementation based on serum carnitine levels. Even in patients with higher weights, there were a certain percentage of patients who had low carnitine levels without supplementation. The literature indicates that most pediatric patients on carnitine-free PN have low carnitine levels within 7 to 10 days without carnitine supplementation. These data from the literature prompted the implementation of a protocol at our institution to check serum carnitine in patients with carnitine-free PN at 7 days. Based on this carnitine level, carnitine was either started or not added to the patient's PN.

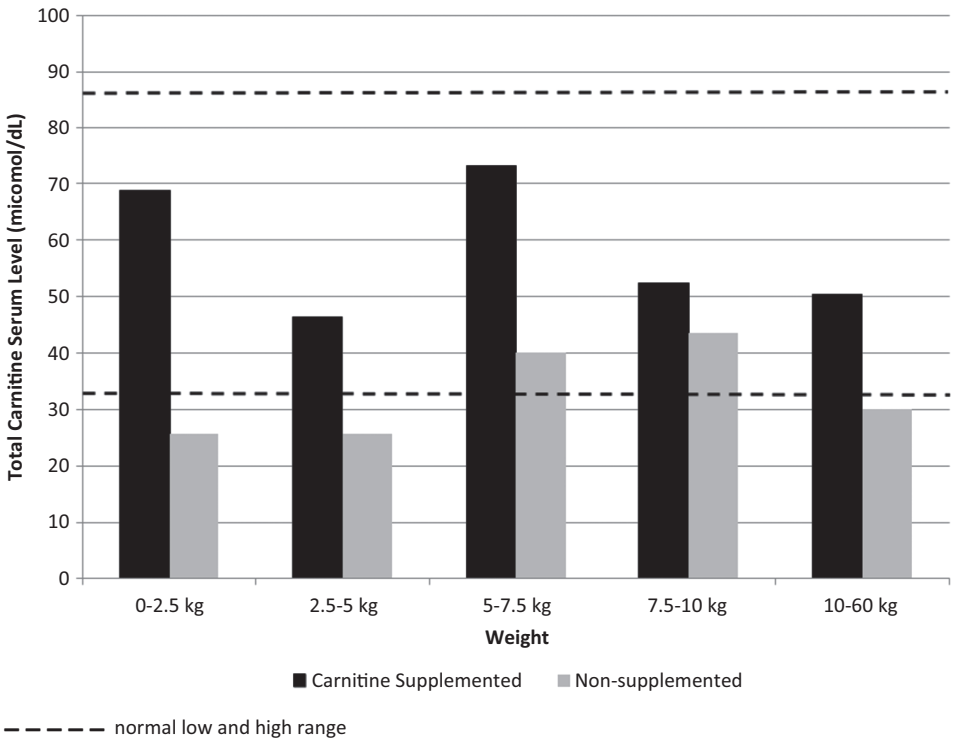

Figure 2. Average total serum carnitine levels in infants by weight in carnitine supplemented and nonsupplemented patients.

Due to our results, we have changed the practice at our institution. Patients who weigh less than 5 kg and are on PN are supplemented with carnitine at 15 mg/kg/day. A carnitine level is checked at 4 days of PN to determine whether carnitine supplementation needs to be continued, discontinued, or the dose adjusted. For patients weighing more than 5 kg who are going to be on PN for longer than 7 days or are medically compromised, carnitine levels are drawn after 7 days. If the patient's carnitine level is low, thus indicating a deficiency, carnitine is added to the PN at 15 mg/kg/day. Carnitine levels are monitored monthly thereafter.

The findings from our study changed our hospital's monitoring and ordering of carnitine. We updated our computerized physician order entry system for PN. We added hard stops on ordering carnitine and provided education windows explaining the new policy for ordering carnitine in PN.

Before this study, we often assumed an association between glucose and triglyceride levels and carnitine stores in our patients. Our hypothesis was that high triglyceride and low glucose levels were associated with low carnitine levels. Our data indicate that there is no statistical association between triglyceride, glucose, and carnitine levels; this is in agreement with the study by Dahlstrom et al.[7] Carnitine levels (free, esterified, and total) should be monitored to assess for carnitine deficiency.

CONCLUSION:

After reviewing the retrospective data from our institution, we suggest that patients weighing less than 5 kg should be supplemented with carnitine. A serum carnitine level should be drawn within 4 days of supplementation to assess whether dose adjustment should be made. Patients who are not supplemented with carnitine should have serum levels drawn within 7 days to determine whether they require supplementation. Carnitine supplementation should be based on serum levels.

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