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Carnitine deficiency in children receiving continuous renal replacement therapy

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Abstract

Carnitine deficiency is known to occur in chronic hemodialysis; however, the effect of continuous renal replacement therapy (CRRT) on carnitine homeostasis has not been studied. We hypothesized that children receiving CRRT are at risk for deficiency because of continuous removal, absent intake, decreased production, and comorbidities related to critical illness. Records of patients with acute kidney injury receiving CRRT at Children's National Health System between 2011 and 2014 were reviewed for total carnitine (TC), free carnitine (FC), feeding modality, severity of illness, and survival outcome. The proportion of carnitine-deficient patients at baseline, 1, 2, and ≥3 weeks on CRRT were compared by chi-square, and relationships with other variables assessed by Pearson's correlation and logistic regression. The study group included 42 CRRT patients, age 7.9 + 1.1 years. At baseline, 30.7% and 35.7% of patients were TC and FC deficient. Within 1 week, 64.5% ($P = 0.03$) and 70% ($P = 0.03$) were TC and FC deficient, and prevalence of deficiency increased to 80% ($P = 0.01$) and 90% ($P = 0.008$) by 2 weeks; 100% of patients were TC and FC deficient after being on CRRT for ≥3 weeks ($P = 0.005$ and $P = 0.01$, respectively, vs. baseline). TC and FC levels negatively correlated with days on CRRT ($r = -0.39$, $P = 0.001$ and $r = -0.35$, $P = 0.005$). Patients with TC and FC deficiency had 5.9 and 4.9 greater odds of death than those with normal levels ($P = 0.02$ and $P = 0.03$). Carnitine is significantly and rapidly depleted with longer time on CRRT, and carnitine deficiency is associated with increased mortality. Consequences of deficiency and benefits of supplementation in the pediatric CRRT population should be investigated.

Key words: Acute kidney injury, pediatrics, CRRT, nutrition

INTRODUCTION

Carnitine is a small molecular weight (161.2 Da) quaternary amine solute that is water-soluble and nonprotein bound.[1] It is derived primarily from the diet (75%), but can also be synthesized in the kidney and liver (25%). The key function of carnitine is to facilitate the transport of fatty acids into the mitochondria for cellular energy production in skeletal and cardiac muscle, where it also plays a pivotal role in protecting myocyte cell membranes from oxidative damage.[2] The total plasma carnitine pool is comprised of both free carnitine molecules and acyl carnitine esters, which vary in size based on chain length. Free plasma carnitine is small and easily dialyzed, with levels decreasing by 60–70% during the course of a single 3-hour hemodialysis session. The ability of hemodialysis to remove acyl carnitines decreases with increasing acyl carnitine chain length.[1] Chronic hemodialysis sessions therefore result in a progressive decline in plasma and muscle carnitine levels over time, with concurrent accumulation of harmful long-chain acyl carnitine compounds. The duration of dialysis is negatively correlated with plasma and muscle carnitine stores.[3] Consequences of carnitine deficiency may include hypoglycemia,

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dyslipidemia, muscle weakness, rhabdomyolysis, cardiomyopathy, arrhythmia, and sudden death.[4]

The carnitine status of pediatric patients with acute kidney injury (AKI) undergoing continuous renal replacement therapy (CRRT) has not been previously studied. Patients undergoing CRRT in the intensive care unit setting may be at increased risk for carnitine deficiency because of its continuous removal, lack of carnitine production by the kidney and/or liver, and absence of carnitine intake (because of prolonged inability to eat by mouth and dependence on carnitine-free total parenteral nutrition [TPN]). Comorbidities related to underlying critical illness, such as trauma, sepsis, toxic shock, multiorgan failure, and systemic inflammatory response syndrome, may also predispose patients to carnitine deficiency.[5]

The purpose of this study was to investigate carnitine deficiency in critically ill children and young adults with AKI undergoing CRRT in the intensive care unit setting. We hypothesized that CRRT, which removes carnitine continuously for twenty-four hours per day, would increase the risk for carnitine deficiency in this already vulnerable population.

SUBJECTS AND METHODS

In 2011, our center instituted a protocol of total and free carnitine monitoring in children undergoing CRRT at periodic intervals. We reviewed the medical records of all patients (age 0–26 years) with acute kidney injury who underwent CRRT at Children's National Health System between 2011–2014 to evaluate the prevalence of carnitine deficiency and risk factors for this deficiency in this population. Patients with End Stage Renal Disease (ESRD) and those patients receiving any carnitine supplementation (including by mouth, intravenous, or in TPN) were excluded. Standard TPN solutions do not include carnitine. Additional data collected from the medical records included diagnosis, length of intensive care unit (ICU) stay, feeding modality, triglyceride level and survival outcome. Data required for calculation of the Pediatric Logistic Organ Dysfunction-2 score (PELOD-2, a validated tool for assessment of the severity of multiple organ dysfunction syndrome in critically ill children), were also collected. This included the following indicators: neurologic (Glasgow Coma Score, pupillary reaction), Cardiovascular (lactatemia, mean arterial pressure), renal (creatinine at initiation of CRRT), respiratory (PaO2, PaCO2, ventilation), and hematologic (WBC count, platelets). The PELOD-2 score and probability of death on the day of carnitine measurement was calculated according to the previously published method.[6]

Table 1 Age-specific reference ranges for total and free carnitine

Age group	Total carnitine* Normal range	Free carnitine* Normal range
1 day	23–68	12–36
2–7 days	17–41	10–21
8–31 days	19–59	12–46
32 days–12 months	38–68	27–49
13 months–6 years	35–84	24–63
7–10 years	28–83	22–66
11–17 years	34–77	22–65
> or =18 years	34–78	25–54

*Values expressed as μmol/L.

Statistical analyses were performed with STATA 11.0 (StataCorp LP, College Station, TX, USA). The prevalence of carnitine deficiency was determined, with deficiency defined as presence of a total or free carnitine value below the age-specific reference value of Children's National Health system laboratory, which are based on the universal reference ranges developed by Mayo Medical Laboratories (see Table 1).[7] The proportion of carnitine-deficient patients at baseline (day of initiation of CRRT), week 1, week 2, and ≥3 weeks on CRRT were compared using chi-square test. Additionally, the prevalence of carnitine deficiency among critically ill patients who were in the ICU for > 2 weeks but not receiving CRRT was compared with prevalence of deficiency amongst patients who received CRRT for > 2 weeks by chi-square test. Relationships between carnitine deficiency and other variables were assessed by Pearson's correlation and multivariable logistic regression.

The study was approved by the Children's National Health System Institutional Review Board, and the study was conducted in accordance with the ethical standards of the Declaration of Helsinki.

RESULTS

Demographics and clinical characteristics

The demographics and clinical characteristics of the study group are shown in Table 2. The CRRT group consisted of 42 patients, mean age 7.9 + 1.1 years (95% CI 5.6–10.1), range 0–26 years. There were 22 males and 20 females (15 African American, 15 Caucasian, and 12 others). The most common causes of acute renal failure were related to bone marrow transplant (38%), congenital or acute heart disease (23.8%), and sepsis (19%). The specific mode of

Table 2 Demographics and clinical characteristics of study group

Characteristic (n = 42 patients)	Value
Age (mean ± SEM, 95% CI)	7.9 ± 1.1 years
Gender	22 male, 20 female
Race	15 AA, 15 Caucasian, 12 other
Primary diagnosis	16 bone marrow transplant 10 congenital/acute heart disease 8 sepsis 3 drug-induced AKI 1 trauma 1 lupus nephritis 1 uric acid nephropathy 1 hypoxic AKI 1 other
PELOD-2 score (mean ± SEM, 95% CI)	11.2 ± 0.43 (10.3–12.1)
Survival rate	12/42 (28.5%)
Length of ICU stay (mean ± SEM, 95% CI)	68.9 ± 10.4 days (48.0–89.9)
Nutrition administration	7 enteral, 35 parenteral

AA = African American; AKI = acute kidney injury; CI, confidence interval; ICU = intensive care unit; PELOD-2 = Pediatric Logistic Organ Dysfunction-2; SEM = standard error of the mean.

CRRT received by all of the study patients was continuous veno-venous hemodiafiltration with total dialysis and filter replacement fluid rate of 2000 mL/1.73 m^2/h. The majority of patients (83.3%) were receiving parenteral nutrition, and the remaining 16.7% were receiving enteral nutrition support. Of 20 patients who had triglyceride levels measured, 45% had hypertriglyceridemia (>250 mg/dL).

Total and free carnitine

At baseline, the mean TC level of the study group was 39.0 ± 5.5 μmol/L. TC declined to 26.8 ± 2.9, 21.9 ± 3.9, and 8.0 ± 2.02 μmol/L, at 1, 2, and ≥3 weeks duration of CRRT. The baseline FC level of the study group was 25.2 ± 4.4 μmol/L. FC declined to 18.7 ± 2.3, 14.5 ± 32.6, and 4.8 ± 4.09 μmol/L, at 1, 2, and ≥3 weeks duration of CRRT.

The prevalence of total and free carnitine deficiency, according to age-specific reference values, significantly increased with time on CRRT (Figure 1). At baseline, 30.7% of patients were TC deficient and 35.7% were FC deficient. Within 1 week of CRRT therapy, the proportion of patients deficient in TC and FC was 64.5% (P = 0.03)

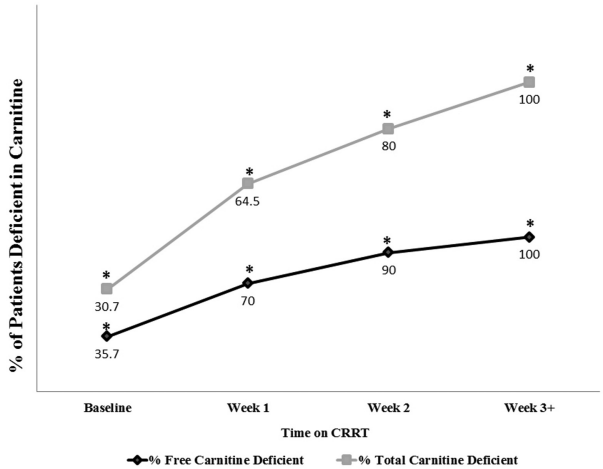

Figure 1 The proportion of patients with total and free carnitine deficiency increases significantly with time on CRRT, from approximately one-third of patients at baseline to 100% of patients after 3 weeks on CRRT (*P < 0.05 compared with baseline). CRRT = continuous renal replacement therapy.

and 70% (P = 0.03), respectively. The prevalence of TC deficiency further increased to 80% and 100% at 2 and 3 weeks on CRRT (P = 0.01 and P = 0.005, respectively, compared with baseline). The prevalence of FC deficiency increased to 90% and 100% at 2 and ≥3 weeks on CRRT (P = 0.008 and P = 0.01, respectively, compared with baseline).

The mean duration of CRRT therapy at time of last carnitine value was 7.8 ± 1.5 days (95% CI 4.6–11.0). Total and free carnitine levels negatively correlated with the number of days on CRRT (r = –0.39, P = 0.001 and r = –0.35, P = 0.005, respectively). The length of ICU stay prior to initiation of CRRT was 19.1 ± 4.6 days (95% CI 9.6–28.5). Among a subset of six critically ill patients hospitalized in the ICU but not receiving CRRT for 30.1 + 12.0 days, 33% were TC and FC deficient. In comparison with patients who received CRRT for a similar duration of time (25.4 + 4.1 days, P = 0.6), the proportion of TC and FC deficiency was significantly higher in those receiving CRRT vs. those not receiving CRRT (82 ± 0.11% vs. 33 ± 0.19% TC deficiency and 91 + 0.08% vs. 33 + 0.19% FC deficiency, P = 0.04 and P = 0.01, respectively).

The total length of ICU stay of the entire study population was 68.9 ± 10.4 days (95% CI 48.0–89.9). The severity of illness of the population determined by PELOD-2 score ranged from 2 to 19 (mean 11.2 ± 0.43), on a scale of 0 to 33 (where 33 indicates maximum severity of illness). The corresponding probability of death

ranged from 0.3% to 91%. Of the 42 patients, only 12 survived (28.5%). There was no significant correlation of baseline total or free carnitine level with length of ICU stay prior to CRRT initiation, total length of ICU stay, PELOD-2 score, or feeding modality.

Patients with total carnitine deficiency had odds ratio of 5.9 for death compared with those with normal TC levels, correcting for age, sex, and race (P = 0.02). Those with free carnitine deficiency had odds ratio of 4.9 for death compared with patients with normal FC levels (P = 0.03).

DISCUSSION

Evidence suggests that carnitine deficiency can be present in critically ill patients because of a myriad of factors intrinsic to their severe illness. A recent study of 30 critically ill adults found that serum carnitine level correlated with disease severity and prolonged hospital stay.[8] A number of experimental and clinical studies in adults have demonstrated alterations in carnitine metabolism and carnitine deficiency in septic conditions.[9] Little is known about the carnitine status of critically ill children, and this has not been previously investigated in those receiving CRRT. There is evidence to show that CRRT efficiently removes other nutritional molecules, including essential amino acids, vitamins, and minerals. Despite inclusion of these nutrients in standard TPN solutions, both children and adults on CRRT require supraphysiological levels of supplementation to replete these losses.[10,11] Preliminary data from a pilot study on the kinetics of carnitine removal in adults receiving continuous veno-venous hemofiltration (CVVH) indicated complete passage and efficient removal of free carnitine through the CVVH membrane, based on calculated sieving coefficients.[12] The clearance of varying chain lengths of acyl carnitine by CRRT is unknown. Given the rapid clearance of free carnitine by CRRT, combined with the lack of carnitine in standard TPN formulations, the potential for carnitine deficiency and need for supplementation in this population may be profound.

In our pediatric population, we found that approximately one-third of patients had carnitine deficiency at baseline, prior to initiation of CRRT. Over time on CRRT, carnitine levels rapidly declined, as the proportion of patients with both total and free carnitine deficiency rapidly increased. We found that about two-thirds of patients were carnitine deficient after just 1 week, 80% at 2 weeks, and 100% beyond 3 weeks of initiation of CRRT. As we hypothesized, continuous removal of carnitine resulted in increasingly severe carnitine deficiency, which correlated with the number of days the patient remained on CRRT. The levels of total and free carnitine decreased progressively with increasing duration of CRRT. The presence of total and free carnitine deficiency was associated with increased risk of mortality in our population.

While not the primary focus of our study, we were able to perform an analysis of the carnitine status of a small subset of critically ill patients who had an ICU stay of at least 2 weeks but did not receive CRRT compared with those who received CRRT for 2 weeks; both groups had comparable ICU stay at the time of carnitine measurement. n. The total and free carnitine status of patients not on CRRT was significantly better than those who received CRRT, suggesting that the impact of critical illness alone on carnitine depletion is not as rapid or severe as the impact of CRRT. Prospective randomized controlled trials are needed to verify this finding.

Our small sample size may have limited our ability to detect more subtle associations of carnitine deficiency with variables such as severity of illness and feeding modality. Another limitation of our study is that we did not measure plasma acylcarnitine profile and therefore were unable to evaluate the effect of CRRT on the various chain-lengths of acylcarnitines.

To our knowledge, ours is the first study to investigate carnitine deficiency in patients receiving CRRT. One case report of carnitine deficiency in a critically ill adult undergoing a prolonged course of CRRT has been recently described in the literature.[5] After approximately 4 months of CRRT therapy, this patient was found to have a low plasma free carnitine of 11 μmol/L (normal range 18–48 μmol/L), and associated alterations in lipid metabolism and massive muscle catabolism. Following initiation of supplementation with 33 mg/kg of intravenous (IV) carnitine daily, the authors report that subsequent plasma carnitine correction was associated with normalization of triglycerides, lactic acid levels, and long-chain acylcarnitine plasma profile in this patient.

The consequences of carnitine deficiency in critically ill children may be severe, as impairment of energy production caused by carnitine deficiency may further increase the risk of cardiac morbidity in this high-risk group of critically ill children receiving CRRT.[13] Because carnitine plays a key role in supplying energy to the myocardium, repletion of muscle carnitine stores is critical in children who are at high risk for both carnitine deficiency and cardiac complications.

Plasma carnitine levels can be quickly and safely repleted with IV carnitine supplementation. Numerous previous studies in carnitine-deficient adults on chronic hemodialysis (HD) have shown improved cardiac function in response to carnitine supplementation.[13–16] We recently

demonstrated improvement in left ventricular (LV) function in a group of children on chronic HD (improved longitudinal strain rate) in response to IV carnitine supplementation compared with a control group of children on HD not supplemented with carnitine.[17]

Emerging evidence also suggests that carnitine supplementation results in improved outcomes in the setting of critical illness, including sepsis[9] and acute heart failure.[18] In septic rats, supplementation with carnitine resulted in decreased severity of illness, faster recovery, improved lipid metabolism, and increased survival rates.[9] Limited clinical data has demonstrated improved respiratory function and hepatic lipid metabolism in septic adults compared with controls.[9]

In light of the high rate of carnitine deficiency in children receiving CRRT, and high risk of morbidity and mortality in this population, we are currently conducting a clinical trial to investigate the effects of carnitine deficiency and supplementation on myocardial function in children receiving CRRT (www.clinicaltrials.gov, NCT01941823). Additional consequences of carnitine deficiency and possible benefits of carnitine supplementation for improving outcomes in this critically ill population should be further investigated.

DISCLOSURES

We did not receive any grant or funding in conduction this study. Sigma Tau is a supporter of another prospective investigator-initiated research study, Effect of Carnitine Deficiency on Myocardial Function in Children Receiving CRRT (ClinicalTrials.gov Identifier: NCT01941823).

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