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Original article

Plasma free carnitine in severe trauma: Influence of the association with traumatic brain injury

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ABSTRACT

Background: Metabolic response to severe trauma requires early nutritional resuscitation. Carnitine is essential for lipolysis, the energy source during this hypercatabolic phase. However L-carnitine is not present in nutritional replacement solutions. Furthermore, free carnitine depletion, defined as carnitine plasma level under 36 μmol/L, was not adequately reported in adult patients with severe trauma. The aim of this study was to assess plasma free carnitine levels and factors of variation in severe trauma.
Method: Our observational study concerned 38 trauma patients including 18 with traumatic brain injury (TBI). On the third day after trauma, plasma free carnitine concentration was determined (by enzymatic method) while patients received artificial nutrition.
Results: Low plasmatic free carnitine concentration was evidenced in 95% of the patients with a median value of 18 μmol/L (11–47). Univariate analysis showed that mean arterial pressure, serum urea, CKD-EPI and patients with TBI were significantly associated with plasma free carnitine concentration less than 18 μmol/L. Lower plasma free carnitine concentration was observed in the group of patients with TBI with 17.72 μmol/L (11–36) versus 21.5 μmol/L (11–47) for others patients ($p = 0.031$). Logistic regression analysis showed that severe trauma with TBI and CKD-EPI above 94 mL/min/1.73 m2 appeared to be independent predictor of lower free carnitine plasmatic concentration (Goodness of fit = 0.87 and AUC = 0.89).
Conclusion: Our observations support hypotheses that plasma free carnitine concentration is lowered in severe injured patients especially for TBI patients and patients with estimated GFR above 94 mL/min/1.73 m^2.

Introduction

Multiple trauma patients present, in the early phase, a major energy expenditure, involving hypercatabolism with muscular proteolysis, lipolysis and micronutrient deficiency [1–3]. An imbalance between energy expenditure and nitrogen intake causes an increase in morbidity and mortality [4–6]. Many studies have shown that early enteral nutrition decreases infections occurrence and severity of organ failure explaining international guidelines which advocate early supplementation [7–14]. Few studies have evaluated the role of carnitine in severe trauma [15–17].

Carnitine is a key element in the lipid metabolic pathway and is required for long chain fatty acids oxidation. In humans, 75% of the intake of carnitine is provided by food and 25% comes from liver, kidneys and brain biosynthesis [18,19] but nutritional replacement solutions do not contain it. Plasma free carnitine which accounts for 80–85% of total carnitine is physiologically between 36 and 46 μmol/L (laboratory standard). Carnitine is mainly eliminated by glomerular filtration and less than 5% of filtered carnitine is excreted [20,21]. Carnitine has an important role in facilitating long-chain fatty acid transport from cytosol into mitochondria for β-oxidation and energy production [18,19].

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Neuroprotective effects have been attributed to carnitine [22] which is also involved in cellular metabolism [23,24]. Primary and secondary deficiencies are known in numerous situations such as prematurity, acute kidney injury, liver failure, hemodialysis, malnutrition and exclusive parenteral nutrition. [25,26] Carnitine deficiency is a metabolic state in which carnitine concentrations in plasma and tissues are less than the levels required for normal function in the organism. Biologic effects of low carnitine levels may not be clinically significant until they reach less than 10–20% of normal [18–21]. Specific consequences of carnitine deficiency are multiple. Excessive lipid accumulation occurs in muscle, hearth and liver. Cardiac and skeletal myopathy can happen, associated with hepatomegaly. Long-chain acylcarnitines are also toxic and may have arrythmogenic effect [23,24]. Few studies have shown a decrease of plasma carnitine and an increase of its excretion in a small number of critical patients [15–17,27–29].

The aim of this study was to assess plasma free carnitine levels and factors of variation in severe injured patients during initial management and after hemodynamic stabilization.

Material and methods

Our observational study involved 38 adults severe injured patients hospitalized in our ICU (Rangueil University Hospital, Toulouse, France) over a 2-year period. Assays were performed on blood samples remaining after routine daily blood tests. No additional blood samples were necessary.

The study protocol was approved by our Institutional Ethics and Research Committee (n°: 34-0513). Since the demographic, physiology, and in-hospital outcome data analyses are used routinely without additional blood samples and did not modify existing diagnostic or therapeutic strategies, the need for written consent was waived.

Clinical features

Severity scores, SAPS II, ISS and TRISS, were recorded for each patient at inclusion.

Body weight, height and body mass index (BMI) were calculated for each patient. Ideal body weight was calculated using the Devine formula and lean body mass was estimated according to the equations defined by Green [30].

Pathology data

Clinical and pathology data were collected on the third day after admission. Quantitative measurement of carnitine was performed by the biochemistry laboratory from routine pathology assessments of patients. Blood samples were collected into heparinized tubes and immediately centrifuged to obtain plasma. Each sample was transferred to two containers at −20 °C until analysis. Plasma free carnitine concentration was determined using filtration enzymatic method (spectrophotometric) with carnitine O-acetyltransferase (CAT) and acetyl coenzyme A (Sigma Chemical Co, UK; BIOSENTEC, France). The reaction between the carnitine and acetyl-CoA in the presence of acid 5,5-dithiobis-2-nitrobenzoic acid (DTNB, also known as Ellman's reagent) generates a chromogenic compound that can be detected at 415 nm [31,32].

Glomerular filtration rate (GFR) was estimated using the CKD-EPI formula [33].

Nutritional management

Most of the study patients received, except when contra-indicated, primarily enteral nutrition within the first 48 h , with a target calorie for nitrogen intake of 25 Kcal/Kg/day.

Statistical analysis

Data were presented as median and range or ratio. A Spearman's rank correlation test was used to analyze the relationship between plasma free carnitine concentrations and both clinical parameters.

Patients were divided in two groups on the basis of their lowest plasma free carnitine concentration according to a cut-off value corresponding to the median value of free carnitine plasma concentrations 18 μmol/L. To compare the different parameters in relation to the free carnitine plasma concentration groups, parametric and non-parametric tests were applied as appropriate. Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the discriminating power of each variable in relation to patients with free carnitine levels of <18 μmol/L. The optimal threshold with its corresponding likelihood ratios (negative and positive) were defined by Youden's index. For each significant variable, the gray zone was determined using a two-step procedure as described by Cannesson.

Finally, independent risk factors for free carnitine plasma deficiency during the first 72 h were sought, by including in a stepwise multivariate logistic regression model the all continuous variables, or their cut-off values, with a $p < 0.2$ in the preliminary univariate analysis. Collinearity was investigated, and if present, the less strongly associated variable was eliminated. Goodness of fit of the model was assessed using the Hosmer-Lemeshow test.

Statistical analysis was performed using Medcalc (MedCalc Software, Ostend, Belgium). A p-value ≤ 0.05 was considered statistically significant.

Results

Thirty-eight patients of whom 10 women were included. Median age was 40 (16–76) years old. Median SAPS II was 48.5 (12–64) and median ISS 29 (10–66). Patients were ventilated in 81% of cases (9 (0–65) days). ICU length of stay was 18 (4–91) days.

ICU admission was prompted by severe injuries with visceral and/or bone lesions in 53% of cases (20 patients, 5 with bone lesions alone and 15 with bone and visceral lesions). Traumatic brain injury (TBI) was associated in 18 cases.

At ICU admission, brain injured patients had a median Glasgow Coma Scale (GCS) score at 6 (3–15). For the other 12 brain injured patients, ICU stay was calculated to be 17.5 (5–91) days.

Nutritional replacement solution was started from the second or third day after admission in 33 patients: 24 patients received enteral nutrition, 2 patients received parenteral nutrition, and 7 received mixed nutrition (from day 5). Five trauma patients did not receive nutritional replacement solutions because oral nutrition was possible from day 4.

Plasma free carnitine concentration levels were below normal in 95% of our patients with a median value of 18 μmol/L (11–47). Coefficient of variation of free carnitine was 38%. Only 2 patients had free plasmatic carnitine within the normal range with 36 and 47 μmol/L respectively. Creatinine clearance was measured in only 28 patients (median 137.5 mL/min/1.73 m^2 (27–347)) using the CKD-EPI equation. A relationship was observed between free plasmatic carnitine concentrations and the following parameters: BMI ($p = 0.049$), mean arterial pressure (MAP) ($p = 0.0154$), estimated GFR ($p = 0.0171$) and serum urea ($p = 0.0022$).

Comparison between the two groups, according to carnitine level are set out in Table 1.

MAP, serum urea, CKD-EPI and the number of patients with TBI were statistically different.

Patients were also statistically different in the two groups regarding initial Glasgow Coma Scale and Abbreviated Head Injury Scale.