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Protein needs of critically ill patients receiving parenteral nutrition

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Abstract

Background: **assess whether the current protein intake recommendations may improve the biochemical parameters of critical patients receiving parenteral nutrition.**

Methods: **longitudinal study with three evaluations made (during the first 72 hours, on the 7th and the 14th days of PN). The following tests were applied: albumin, C-reactive protein, prealbumin, total cholesterol, HDL, triglycerides, lymphocytes, and glutathione peroxidase. The severity was determined by SOFA. The statistical analysis included the Spearman and Mann-Whitney tests, as well as ANOVA (analysis of variance).**

Results: **among the 53 patients evaluated, 20 (37.74%) died. The mean calorie was 24.68±9.78 kcal/kg (beginning of PN), 26.49±8.89 kcal/kg (3rd to 7th days of PN), and 30.9±12.19 kcal/kg (7th to 14th days of PN). The mean protein was 1.19±0.44 g/kcal/kg (first 72 hours of PN), 1.29±0.44 g/kcal/kg (3rd to 7th days of PN) and 1.49±0.69 g/kcal/kg (7th to 14th days of PN). Prealbumin, albumin, total cholesterol and HDL were below the reference values, while the CRP levels were high. Throughout the three evaluation times, there was no a significant improvement on the levels of laboratory examinations. A strong and negative correlation was found between SOFA and prealbumin (r=-0.64, p=0.05).**

Conclusions: **the protein offer, according to the traditional recommendations, was not enough to improve the biochemical parameters of critical patients undergoing parenteral nutrition.**

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Key words: *Parenteral nutrition. Intensive care unit. Protein.*

LAS NECESIDADES PROTEICAS DE PACIENTES EN ESTADO CRÍTICO QUE RECIBEN NUTRICIÓN PARENTERAL

Resumen

Introducción: **evaluar si las recomendaciones de ingesta de proteínas actuales pueden mejorar los parámetros bioquímicos de los pacientes críticos que reciben nutrición parenteral.**

Métodos: **estudio longitudinal con tres evaluaciones realizadas (durante las primeras 72 horas, en el séptimo y los días decimocuarto de nutrición parenteral). Se aplicaron las siguientes pruebas: albúmina, proteína C reactiva, prealbúmina, colesterol total, HDL, triglicéridos, linfocitos y glutatión peroxidasa. La gravedad se determinó por SOFA. El análisis estadístico incluyó las pruebas de Spearman y Mann-Whitney, así como ANOVA (análisis de varianza).**

Resultados: **de los 53 pacientes evaluados, 20 (37,74%) fallecieron. La caloría media fue de 24,68±9,78 kcal/kg (comienzo de PN), 26,49±8,89 kcal/kg (tercero-séptimo días de PN), y 30,9±12,19 kcal/kg (séptimo-décimo cuarto días de PN). La proteína media fue de 1,19±0,44 g/kcal/kg (primeras 72 horas de PN), 1,29±0,44 g/kcal/kg (tercero-séptimo días de PN) y 1,49±0,69 g/kcal/kg (séptimo-decimocuarto días de PN). La prealbúmina, la albúmina, el colesterol total y la HDL estaban por debajo de los valores de referencia, mientras que los niveles de PCR eran altos. A lo largo de los tres tiempos de evaluación, no hay una mejora significativa en los niveles de los exámenes de laboratorio. Una correlación fuerte y negativa entre SOFA y prealbúmina (r=-0,64, p=0,05).**

Conclusiones: **la oferta de proteínas, de acuerdo con las recomendaciones tradicionales, no fue suficiente para mejorar los parámetros bioquímicos de los pacientes críticos sometidos a nutrición parenteral.**

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Palabras clave: *Nutrición parenteral. Unidad de cuidados intensivos. Proteína.*

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Introduction

Total or partial parenteral nutrition (PN) is necessary when the enteral nutrition (EN) may not be used or does not meet the needs of patients[1]. In general, using nutritional support is challenging on an intensive care unit[2].

Patients who received care on an intensive care unit (ICU) do not characterize a homogeneous group, since diagnostics and complication degrees vary[3]. However, the aggression, whether infectious or not, creates a body response that is similar to stress or trauma. This response is commonly referred to as systemic inflammatory response syndrome (SIRS) with a major involvement of oxidative stress. It results from an excessive production of oxidant substances (free radicals) that require a major production of antioxidants, such as glutathione peroxidase (GPx)[4].

In the case of SIRS, there is a strong glyconeogenesis with mobilization of amino acids from the skeletal muscle, conjunctive tissue and viscera to repair tissues and for immunity stimulation (synthesis of immunoglobulins, acute phase proteins), characterizing hypercatabolism[5]. Considering this great mobilization of protein reserves, the nutritional support is notoriously important.

Considering that previous studies indicate that the amount of protein offered may influence the clinical condition of the critical patient[2-6], the objective of this study was to evaluate whether the current protein intake recommendations may improve the biochemical parameters of critical patients receiving parenteral nutrition.

Methods

This longitudinal study was conducted with patients using PN, admitted to the ICU of a tertiary hospital of Campinas, SP, Brazil. This study was approved by the Ethics Committee of the School of Medical Sciences of UNICAMP. The evaluations were conducted on three different times (during the first 72 hours of PN, on the 7th and 14th days). Patients were monitored up to the end for prognostic evaluation (hospital discharge and death or admission time superior to 8 months – limit date for data collection).

The criteria to participate in the research were: ICU admission, use of PN indicated by the physician responsible for the patient and filling out the free and clear consent term.

The body mass index (BMI)[7] was calculated from the weight and height values that were measured according to Lohman, Roche and Martorell[8]. When the patient showed an edema, the weight of the edema was subtracted from the total body weight, as recommended by Duarte Castellani[9].

In circumstances where it was not possible to determine the body weight due to bed rest, an indirect method was used to estimate the body weight according to Chumlea et al.[10]. Similarly, in order to estimate the height, the arm spread was considered, according to Mitchell & Lipschitz[11], and the knee height, as suggested by Chumlea, Steibaugh & Guo[12].

The anthropometric evaluation was conducted by an adipometer (Lange Skinfold Caliper®), a stadiometer, a digital scale (Lider®) with capacity for 300 kg, and an inextensible tape measurement with 0.1 cm precision.

The albumin, C-reactive protein (CRP), prealbumin, total cholesterol, HDL cholesterol, triglyceride (TGL) and lymphocyte levels were dosed at the Laboratory of Clinical Pathology of the Hospital, using the following methods, respectively: colorimetric (bromocresol green), nephelometry, enzymatic colorimetric, direct enzymatic colorimetric, enzymatic colorimetric and automated global count (electronic counter) / differential count by microscopy automation.

Regarding glutathione peroxidase (GPx), the dosage was performed in the Exercise Laboratory of the Institute of Biology, Unicamp, based on the technique proposed by Paglia and Valentine[13]. The Randox Laboratory's RANSEL (RS504) ® kit was used to determine the GPx, which was analyzed from a 1 ml blood sample collected in a heparinized vial, stored at -80ºC. RANSEL RX Daytona at 340nm was used for reading the samples. Randox Laboratory's ransel control (SC692) ® was used as a control.

Reference values: prealbumin 20 - 40 mg/dL, albumin 3.5 - 5.2 g/dL, total cholesterol < 200 mg/dL and ≥ 150 mg/dL, CRP ≤ 0.3 mg/dL, GPx 4171 - 10881 U/l, Lymphocytes 1000 - 4000/mm^3, TGL ≤ 150 mg/dL and HDL ≥ 40 mg/dL.

In order to classify the risk of complications (no, low, moderate and high risk of complications), the CRP/albumin relation was used, according to Correa et al[14].

The evaluation of severity was determined by calculating the score of sequential organ failure assessment (SOFA)[15].

The ESPEN recommendations[16] were used to calculate the energy and protein requirement. Subsequently, the sum of macronutrients actually received by parenteral, enteral and oral routes was made.

Statistical treatment of collected data was performed using the statistical analysis system (SAS), version 9.2 software (SAS Institute Inc, 2002-2008, Cary, NC, USA). The Spearman correlation coefficient was used to assess linear association between parameters. The classification of values of this correlation was performed according to Mitra and Lankford[17], considering from 0.30 to 0.40, a weak correlation; from 0.40 to 0.60, a moderate correlation; and over 0.60, a strong correlation.

The Mann-Whitney test was used for comparing variables between two groups (death and no death). In addition, aiming to compare the parameters evaluated,

considering times and the final outcome, the repeated measures of ANOVA with rank transformation was used. A significance level of 5% was adopted.

Results

Fifty-three patients were evaluated (75.47% males and 24.53% females, with average age of 58.14 years old) and 20 patients (37.74%) died.

There was no significant difference dead patients and those who survived in relation to age (p = 0.13). However, there was a significant difference on the SOFA values between the groups (death and no death) (Table I).

A trend was verified, suggesting a higher mortality rate among patients with lower BMI values (p = 0.056) (Table I). According to the BMI, most patients 19/26 (73.1%) had a normal weight and 5/26 (19.2%) were overweight.

There was no significant correlation between SOFA and CRP, SOFA and GPx. However, a negative and strong correlation was found between SOFA and prealbumin (Table II).

Table I
Comparison of markers and inflammatory and nutritional status between the groups I (no death) and II (death)

Variable	*Group*	*N*	*Mean*	*SD*	*P-value*
SOFA0	I	16	3.39	2.80	0.01*
SOFA0	II	10	6.40	2	
CRP	I	32	11.83	8.55	0.73
CRP	II	13	11.70	2.50	
GPx	I	14	4638.78	1229.44	0.63
GPx	II	8	4457.33	3397.30	
Albumin	I	28	2.96	2.68	0.30
Albumin	II	17	2.22	0.47	
Prealbumin	I	29	11.54	6.07	0.34
Prealbumin	II	11	8.83	1.84	
CRP/albumin	I	28	4.54	0.23	0.75
CRP/albumin	II	13	6.24	1.39	
BMI	I	19	23.77	15.89	0.056
BMI	II	7	21.02	16.36	

CRP = C-reactive protein; GPx = glutathione peroxidase; BMI = body mass index
*significance value, p < 0.05 - Mann-Whitney test.

Table II
Statistically significant correlations between nutritional and clinical markers

Correlations	*R-value*	*P-value*	*Classification*
Albumin and BMI	0.41	0.05	Moderate
Albumin and Total cholesterol	0.45	0.00	Moderate
Albumin and prealbumin	0.43	0.01	Moderate
Prealbumin and CRP	-0.43	0.01	Moderate
Prealbumin and CRP/Alb	-0.50	0.00	Moderate
Prealbumin and total cholesterol	0.35	0.04	Weak
Total cholesterol and CRP	0.34	0.03	Weak
Total cholesterol and CRP /Alb	-0.44	0.01	Moderate
Total cholesterol and TGL	0.46	0.00	Moderate
SOFA and prealbumin	-0.64	0.05	Strong

CRP = C-reactive protein; BMI = body mass index

Considering the CRP/albumin relation, 29/41 (70.73%), the patients showed a high risk of complications. Among them, 9 (31.03%) died, 2 (6.9%) remained hospitalized, and 18 (62.07%) were discharged from the hospital. Regarding those patients classified as patients with low or no risk of complications (5/41; 12.2%), all of them were discharged from the hospital.

In patients in general, while the prealbumin, albumin, total cholesterol and HDL cholesterol levels were below the reference levels, the CRP levels were high. Throughout the three evaluation times, there was no statistically significant improvement on the levels of laboratory examinations.

Table III shows the mean calories and macronutrients received by parenteral, enteral or oral nutrition.

Discussion

The negative correlation between the high CRP levels and the low levels of the other examinations (total cholesterol, HDL cholesterol, and prealbumin) characterized the inflammatory process, according with the literature[18,19,20].

We verified a strong correlation of SOFA and prealbumin. On the research by Sullivan, Sun and Walls[21], they observed that patients with low levels of prealbumin showed a higher death rate. This protein is the one that is less affected by hepatic diseases and by the hydration condition[22].

In addition, a low activity of GPx was verified (in the total blood) in most part of the population. Such enzyme, which depends on selenium, is part of the defense mechanism, which, according to the severity of the lesion or the infection, is consumed in a higher amount.

A trend that suggests a higher mortality rate among patients with lower BMI values was verified. It is possible that with a higher sample such correlation is confirmed and, thus, evaluating the nutritional condition through BMI could be considered a prognostic factor.

Other studies[23,24] reported that low BMI values were associated with high mortality.

The CRP/albumin relation was not considered a prognostic instrument. However, all patients classified as low and no risk patients were discharged from the hospital. The CRP/albumin relation is effective to classify the risk of complications[14,25].

During the inflammation process, a hypoalbuminemia condition is common, mainly on critical patients, due to the severe reduction on the protein synthesis and to an increased protein degradation[26].

In our study, the offer of 1,19 ± 0,44 g/kg/day of protein (during the first 72 hours of PN), 1,29 ± 0,44 g/kg/day (3rd to 7th days of PN) and 1,49 ± 0,69 g/kg/day of protein (7th to 14th day of PN) (according to the recommendation by ESPEN[16]) was not enough to improve the levels of prealbumin and other biochemical parameters, throughout the three evaluation times. It is possible that this may have happened due to the persistence of a severe inflammation, as indicated by the consistently high values of CRP.

Gentile et al.[27] state that patients who survive infection, sepsis and the systemic inflammatory response syndrome (SIRS) may progress to persistent inflammation, immunosuppression and catabolism syndrome (PICS), with rare possibilities of reverting the clinical condition.

Despite the fact that not all parameters were collected to diagnose PICS, since this was not the objective of this study, most patients met some of the criteria (admission time > 10 days; albumin < 3; CRP > 150 mg / dL; lymphocytes < 800 / mm^3).

Therefore, it is undeniable that innovative strategies are necessary to rebalance the immunological system, making it possible for the condition to improve and for the patient to recover.

In the area of nutritional support, one of the strategies that is under discussion is the contribution of infusing amino acids for protein synthesis[28].

In a retrospective study, the offer of 1.2 g/kg/day of protein was considered ideal[29]. Another research[30] showed a reduction of catabolism due to the ingestion of protein (1.1-1.5 g/kg/day). Allingstrup et al[31] and Weijs et al[6] reported that the supply of protein (1.2-1.5 g/kg/day) was associated to lower mortality.

Singer et al[2] recommend the initial offer of 1.5 g/kg/day of protein, regardless of the calorie intake. In case

Table III
Mean calories and nutrients received by the patient during the three times of assessment

Time	*Calories*	*Cal/Kg*	*Ptn(g)*	*Ptn/kg*	*CHO(g)*	*CHO/kg*	*Lip(g)*	*Lip/kg*	*Weight (kg)*
Up to 72 h	1595,85 ± 541,24	24,68 ± 9,78	76,85 ± 25,75	1,19 ± 0,44	232,33 ± 84,97	3,49 ± 1,55	49,87 ± 16,95	0,79 ± 0,30	65,92 ± 10,7
3rd to 7th day	1790,32 ± 576,8	26,49 ± 8,89	87,44 ± 29,22	1,29 ± 0,44	263,06 ± 90,06	3,70 ± 1,39	54,06 ± 18,58	0,83 ± 0,24	64,07 ± 12,2
7th to 14th day	1947,33 ± 625,6	30,9 ± 12,19	97,80 ± 30,66	1,49 ± 0,69	283,27 ± 93,23	4,45 ± 1,92	57,27 ± 22,41	0,94 ± 0,24	53,0 ± 4,32

Cal = calorie; Ptn = protein; CHO = carbohydrate; Lip = lipids.

the patients remains under hospitalization, the high protein intake may be combined with the calories to avoid proteolysis.

In a systematic review, the authors refer to the lack of strong evidence, but suggest that offering 2.0-2.5 g/kg/day of protein may be ideal and safe for critical patients[32].

There is a trend in the literature to recommend higher doses of protein to critical patients, however, a point to be explored would be the maximal protein dose that may be administered with no adverse effects and that reflects s noticeable benefits on the laboratory examinations.

Limitations of the study

BMI is imprecise in critically ill patients because their hydration condition may alter the body weight. We tried to minimize the imprecision of the BMI using the recommendation by Duarte & Castellani[9], discounting the weight of the edema found in patients.

To determine the energy requirements, indirect calorimetry is recommended, but, according to ESPEN[16] in the absence of indirect calorimetry, 25 kcal/kg/day of energy is recommended in the initial acute phase, increasing the target over the next 2–3 days.

Conflict of interest

There are no conflicts of interest to declare.

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