Nutr Hosp. 2016; 33(3):528-532 ISSN 0212-1611 - CODEN NUHOEQ S.V.R. 318

ARÁN

Nutrición Hospitalaria

Trabajo Original

Paciente crítico

Timing *versus* caloric goal in nutritional therapy for critically ill patients

Momento de inicio versus *meta calórica en terapia nutricional para pacientes críticos*

Oellen Stuani Franzosi[1] and Sergio Henrique Loss[1,2]

[1]Post-Graduate Medical Sciences Program. School of Medicine. Universidade Federal do Rio Grande do Sul. Porto Alegre. Brazil. [2]Intensive Care Unit. Hospital de Clínicas de Porto Alegre. Porto Alegre, Brazil

Abstract

Introduction: Enteral nutrition is an important therapy for severely critically ill patients. The timing and amount of energy have been highly debated.

Objective: The aim of the present study was to directly compare the timing and the caloric targets in critically ill patients.

Methods: Retrospective cohort study conducted at a single center, comparing timing and caloric goal for critically ill patients. Patients were stratified according to the start of nutritional therapy (24, 48, or more than 48 h) and the amount of energy delivered (target adequacy of previously calculated percentage in the first week). Statistical analysis was performed using parametric and non-parametric tests for independent samples and logistic regression. The results were expressed as mean ± standard deviation or incidence and percentage.

Results and discussion: There were no differences in major clinical outcomes in relation to the achievement of percentage of caloric goal at the end of the first week of the study. The beginning of caloric intake on the first day of hospitalization was associated with reduced mortality in the intensive care unit, but not with hospital mortality. The strategy of an early and limited amount of calories seems to be associated with a better outcome. Prospective studies evaluating and comparing these strategies are recommended.

Key words:

Critical care. Nutrition therapy. Early nutrition. Energy intake. Caloric goal. Mortality.

Resumen

Introducción: la nutrición enteral es una importante terapia para pacientes en estado crítico. La comparación entre el momento de inicio y el aporte calórico ha sido muy debatida.

Objetivo: el presente estudio tuvo como objetivo comparar directamente el momento de inicio y la meta calórica en pacientes críticamente enfermos mediante un estudio de cohorte retrospectivo conducido en centro único.

Métodos: se estratificaron los pacientes conforme el comienzo de la terapia nutricional (24, 48, o más de 48 horas) y la cantidad de energía suministrada (adecuación a la meta de porcentaje que, anteriormente, en la primera semana, se ha calculado). Se realizó el análisis estadístico a través de pruebas paramétricas y no paramétricas para las muestras independientes y de regresión logística. Se expresaron los resultados como la media ± la desviación típica, o la incidencia y el porcentaje.

Resultados y discusión: hasta el final de la primera semana, no hubo diferencias en los principales resultados clínicos en relación con el logro de la meta de porcentaje calórico. Se asoció el inicio de la ingesta calórica en el primer día de hospitalización con la reducción de la mortalidad en la unidad de cuidados intensivos, pero no con la mortalidad hospitalaria. La estrategia de una cantidad temprana y limitada de calorías parece asociarse con un mejor resultado. Se recomienda hacer estudios prospectivos con el fin de evaluar y comparar esas estrategias.

Palabras clave:

Cuidados críticos. Terapia nutricional. Nutrición enteral precoz. Ingestión de energía. Meta calórica. Mortalidad.

Received: 16/01/2016
Accepted: 18/02/2016

Franzosi OS, Loss SH. Timing *versus* caloric goal in nutritional therapy for critically ill patients. Nutr Hosp 2016;33:528-532

Correspondence:

Oellen Stuani Franzosi. Hospital de Clínicas de Porto Alegre. Rua Ramiro Barcelos 2350, Sala 445. 90035-003 Porto Alegre, RS. Brazil
e-mail: oellen.franzosi@gmail.com

INTRODUCTION

Nutritional support is one of the most important therapeutic strategies for properly resuscitated critically ill patients (1). Both timing and energy target of nutritional therapy represent a field of active discussion (2-5). However, the early onset of nutritional therapy, within the first 24-48 hours at the intensive care unit (ICU) after proper resuscitation, and a progression to a predetermined target –generally a caloric target between 20 to 30 kcal/kg/day until the fifth to seventh day– are frequent recommendations from different guidelines and expert opinions (6-12). There are few studies that directly compare timing *vs.* caloric goal regarding critically ill patients and this is the aim of the present study.

METHODS

This is a cohort, retrospective, observational study, conducted at the ICU of Hospital de Clínicas de Porto Alegre (HCPA) from July to October 2011. The aim of the study was to compare outcomes between two strategies of nutrition, namely, early nutrition *vs.* achieving a caloric goal. We included all adult patients (aged 18 years old or above) who remained at the ICU for at least seven days, submitted or not to mechanical ventilation, and could start enteral nutrition therapy in the first 48 hours. Patients already receiving enteral nutrition therapy prior to admission and those with associated oral nutritional therapy were excluded.

The project was approved by the Research Ethics Committee of HCPA, under registration number 110243. Since it is a retrospective study and data were analyzed after patients' discharge, exemption from informed consent was allowed. The authors signed a document to guarantee patients' anonymity in the use of data according to guidelines and regulatory standards for research involving human subjects.

Data collected on admission included age, gender, weight and height (to calculate body mass index [BMI]), diagnosis and Acute Physiology and Chronic Health Evaluation (APACHE II). ICU monitoring data included nutrient dose (parenteral and/or enteral), duration of mechanical ventilation, ICU and hospital length of stay, and ICU and hospital mortality.

Energy dose was individually calculated according to institutional protocol. Basically, adult patients with BMI < 20.5 kg/m^2 and the elderly with BMI < 22 kg/m^2 should receive 30 kcal/kg per day (13). Adults with BMI ≥ 20.5 and < 30 kg/m^2 and normal elderly (BMI ≥ 22 kg/m^2) should receive 25 kcal/kg per day. The goal of protein supply was 1.5 g/kg per day. As far as obese individuals (BMI ≥ 30 kg/m^2) are concerned, specific recommendations were used (12,14). Thus, the caloric intake was estimated at 11 to 14 kcal/kg current weight or 22 to 25 kcal/kg ideal weight. The protein supply was estimated based on the ideal weight: patients with a BMI between 30-40 kg/m^2 should receive $\geq$ 2g/kg of protein and patients with BMI ≥ 40 kg/m^2 should receive ≥ 2.5 g/kg of protein based on ideal weight. The planned calorie dose varied daily, with approximately 30% of the recommended target in the first 24 hours, 60% within 48 hours and 90-100% on the third day.

Patients were divided into four groups: in the first group nutritional therapy was initiated within 24 hours (NT1 group, receiving the first day a calorie amount between 20-30% of the calculated target); the second group of patients received nutritional therapy between 24 and 48 hours (NT2 group, starting on the second day a calorie amount between 20-30% of the calculated target); individuals who started feeding after 48 hours comprised the third group called "late" (NT3); and patients who achieved the calorie target (supply of at least 60% of that planned on the 5th-7th day) formed the RCG (reached caloric goal) group.

Statistical analysis was performed using parametric and non-parametric tests of data collected for independent samples, respecting the distribution of variables by using the Kolmogorov-Smirnov test.

There are overlapping data between timing groups (NT1, NT2 and NT3) and the RCG group, since a given patient in one of the timing groups could belong to the RCG group. Therefore, comparisons in these four groups were performed by logistic regression with patients in groups NT1, NT2 and NT3 subdivided according to the success or failure in achieving energy intake. Thus, for example, data from the NT1 group were conducted in the logistic regression complying with two possible scenarios: patients who were early fed and reached the caloric goal and those who were early fed and did not reach the caloric goal. The same process was applied to NT1 and NT2 groups.

Results were expressed as mean $\pm$ standard deviation (SD) or incidence and percentage. Differences were considered statistically significant at $p < 0.05$. Analyses were performed using IBM SPSS software, version 20.0.

RESULTS

In the study period 357 ICU admissions occurred, 126 met the inclusion criteria and were included in the final analysis. Patients were divided into four groups, according the description on methods session. Table I summarizes and compares demographic analyses between groups, with no significant differences between them (except for gender, considering that there were more women in the NT1 group, and for surgery, with fewer surgical patients in the RCG group). There is no statistically significant difference in ICU and hospital mortality between surgical and non-surgical patients. All patients but one were submitted to MV (and this patient was allocated in NT1 group once she started nutritional therapy on the first day). Length of stay and outcomes are presented in table II and show a significant reduction in mortality in patients fed within the first 24 hours. Among the patients fed within the first 24 hours (NT1), 66.6% achieved caloric goal on the 5th to 7th day. A stratified subgroup analysis based on supply adequacy was conducted within this group (NT1), and no significant differences related to this stratification in terms of mortality were noticed (Table III). Hence, reaching caloric target did not seem to influence the outcome in the early fed group. This

Table I. General characteristic of the study groups

	NT1 (20)	NT2 (67)	NT3 (36)	RCG (64)	p*
Age (years)	58.1 (22.9)	59.8 (16.3)	59.7 (15.7)	57.8 (17.6)	NS
Male	3 (15%)	21 (31.3%)	20 (55.6%)	31 (48.4%)	0.021**
BMI (kg/m^2)	24.9 (12.4)	25.8 (5.8)	26.1 (6.8)	26 (5.4)	NS
Surgery	5 (25%)	16 (23.9%)	12 (33.3%)	10 (15.4%)	0.004***
Noradrenalin[1]	9 (45%)	37 (55.2%)	20 (55.6%)	36 (56.2%)	NS
APACHE II[2]	20.1 (3.42)	22.8 (7.4)	21.8 (9.4)	21.6 (7.2)	NS

*Continuous variables reported as mean and standard deviation; nominal variables reported as incidence and percentage. *ANOVA for continuous variables and Chi^2 with residue analysis for nominal variables; NT1: Nutritional therapy in the first 24 hours with infusion of 20-30% of the dose of calories; NT2: Nutritional therapy started with the infusion of 20-30% of the dose on the second day of calories; NT3: Nutritional therapy started after day 2; RCG: reached calorie goal (energy intake of 60% or more of the previously calculated dose); [1]medium dose greater than or equal to 0.1 mcg/kg/min in the first day; [2]Acute Physiology and Chronic Health Evaluation II; **Significant among NT1 and others; ***Significant between RCG and others; NS: not significant.*

Table II. Differences in outcomes between groups

	NT1 (20)	NT2 (67)	NT3 (36)	RCG (64)	p*
MV (days)	15.5 (8.8)***	15 (8.8)	11.8 (8.4)	14.7(9.8)	NS
LOSh (days)	53.3 (37.4)	34.5 (17.8)	40.9 (26.1)	38.8 (25.6)	NS
Death ICU	3 (15%)	29 (43.3%)	17 (47.2%)	24 (37.5%)	0.001**
Death hospital	7 (35%)	35 (52.2%)	15 (41.7%)	29 (45.3%)	NS

*Continuous variables reported as mean and standard deviation; nominal variables reported as incidence and percentage. *ANOVA for continuous variables and Chi^2 with residue analysis for nominal variables; NT1: Nutritional therapy in the first 24 hours with infusion of 20-30% of the dose of calories; NT2: Nutritional therapy started with the infusion of 20-30% of the dose on the second day of calories; NT3: Nutritional therapy started after day 2; RCG: reached calorie goal (energy intake of 60% or more of the previously calculated dose); MV: mechanical ventilation; LOSh: length of stay at hospital; **Significant among NT1 and other; ***all patients but one were submitted to MV, and this patient started nutrition therapy on day 1, hence, the precise number of NT1 patients in this cell is 19; NS: not significant.*

Table III. Mortality among patients fed the first 24 hours stratified for calorie goal

	NT1R (13)	NT1NR (7)	p
Death ICU	4 (30.8%)	2 (28.6%)	NS
Death hospital	5 (38.5%)	2 (28.6%)	NS

Nominal variables reported as incidence and percentage and analyzed with Chi^2. NT1R: number of patients receiving nutritional therapy in the first 24 hours and reached the caloric goal; NT1NR: number of patients receiving nutritional therapy in the first 24 hours and did not reach the calorie goal; NS: not significant.

type of stratification was also applied to NT2 and NT3 groups for performing the logistic regression in the column with repeated individuals, that is, the RCG column (Table II). An energy supply from 30% to 100% of previous caloric estimation between the 3rd and 7th day of hospitalization analyzed by residuals of Chi^2 did not have an impact on the outcomes. However, a logistic regression model including the most significant variables detected that early (first 24 hours) nutritional therapy remained the only significant variable in terms of reduction in ICU mortality (Table IV).

DISCUSSION

The current study compares direct early nutritional therapy, which is characterized by a more modest supply of energy (20-30% of the calculated target started on the first or second day), *vs.* a caloric goal-oriented strategy (energy repletion equal or higher than 60% of the calculated calorie target). Our data show that properly resuscitated critically ill patients tend to benefit from a start of nutritional therapy within 24 h of ICU admission, being in agreement with data previously reported in the literature (15,16).

We performed an analysis comparing timing of nutritional therapy *vs.* caloric target. The results show that early nutrition was associated with reduction in mortality while achievement of caloric goal previously proposed (60% or more of the previously performed calculation) showed no benefit on outcomes. We consider these data as being very relevant since groups were well matched (there were no significant differences in age, severity score and use of vasopressors). The EDEN Study has reported outcomes regarding the amount of calories administered to patients during the first week in ICU (17). In such study, the aim was to feed the study group with a very low amount of energy (trophic nutrition) during this time. However, we did not compare trophic nutrition *vs.* full nutrition nor trophic nutrition *vs.* time. Our study did not

Table IV. Multivariate analysis of parameters evaluated in the first week of critically ill patients associated with ICU mortality

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	p
APACHE II	21.99 (8.27)	N/A	N/A	N/A	N/A	N/A	N/A	NS
Age (years)	59.6 (16.6)	N/A	N/A	N/A	N/A	N/A	N/A	NS
20-30% dose	S	NS	N/A	N/A	N/A	N/A	N/A	0.044 (0.01-0.93)
40% dose	N/A	N/A	NS	NS	NS	NS	NS	NS
50% dose	N/A	N/A	NS	NS	NS	NS	NS	NS
60% dose	N/A	N/A	NS	NS	NS	NS	NS	NS
90-100% dose	N/A	N/A	NS	NS	NS	NS	NS	NS

Multivariate regression analysis with a 95% confidence interval; continuous parameters expressed as mean and standard deviation. APACHE II: Acute Physiology and Chronic Health Evaluation II; N/A: not applicable; S: variable with statistically significant result in the regression (p value and confidence interval); NS: variable with no statistically significant result in the regression.

attempt to replicate EDEN's strategies regarding nutritional support in our patients, but rather compared the outcomes of patients that started early nutritional intake *vs.* the patients that reached the caloric goal as of the 5th until the 7th day.

We noticed that in the population of clinical patients, supply of calories was significantly higher than in surgical patients. This is not surprising, since impairment in diet progression is often observed in surgical population. A noticeable fact in this study is that there was not a significant measurable benefit in clinical population of patients even when they received more calories.

Critically ill patients are extremely catabolic and consume their nitrogen and carbon atoms mainly stocked in lean mass (muscle) aiming at the synthesis of inflammatory proteins, generation of glucose and other amino acids to infuse energy to systems with high oxygen consumption, healing and inflammatory response (18,19). The consumption of muscle mass is associated with hyperglycemia and immunosuppression with persistent inflammation (20,21). This scenario justifies the early administration of energy and proteins, even though we know that this consumption does not cease with the exogenous nutrients supply (22,23). The amount of calories and the timing of nutritional therapy are currently subject of intense discussion. While several guidelines suggest an early and vigorous protein administration associated with a more modest supply of energy (20-30 kcal/kg/day) (6,8-12,14,23) or even less (24,25), others argue that this energy repletion can wait one week after the patient's hemodynamic resuscitation, also recommending feeding with very low caloric dose, called trophic nutrition (4,5,26,27). This approach would aim at preserving the structure of the digestive epithelium (trophic diet) and at decreasing the translocation of pathogens that perpetuate inflammatory response.

In the first scenario there is clear concern about the reduction of negative energy balance, which would be independently related to worse outcomes of severe inflamed patients. In the second one, the prevailing view is that the body does not properly incorporate nutrients during the acute phase of injury and the goal would be the structural maintenance of the digestive epithelium.

In 2012, our group evaluated the impact of achieving an appropriate percentage of energy and protein on the outcome (28). In this study, a caloric supply equal to or higher than 60% of the calculated target was defined as full diet. Groups (higher and lower than 60% of the calculated target) were very similar at admission and at the end of the observation period there was no superiority of one group over the other (28). Undoubtedly, although this study does not support hypocaloric and trophic feeding – since this strategy was not adopted in this occasion– it does not strengthen the need to achieve full, goal-oriented supply.

This study has some limitations. Being a retrospective cohort study, it has limited the determination of some important parameters on the data analysis, mainly vasopressor dose and length of use. It is a study conducted at a single center, which can limit the extrapolation of data for intensive care units as a whole. Besides, being a retrospective design, it can only produce associative data and, thus, generate hypothesis. We have no indirect calorimetry and because of that we could not parameterize our estimates of energy needs with a gold standard method. Evaluation of body composition was not performed, so that the nutritional state in this study was represented by the BMI, which has limitations in the population of critically ill patients. Furthermore, the sample does not allow an analysis of BMI subgroups. This issue is very important since there are questions regarding the adequacy of energy supply, specifically if it would impact outcomes in the extremes of the population (malnourished and obese individuals). We did not use a specific tool to assess nutritional risk of critically ill patients (such as NUTRIC - Nutrition Risk in Critically ill score) (29). Categorizing critically ill patients according to the nutritional risk would allow the identification of those who most benefit from aggressive nutritional therapy. Finally, because of the design used in this study, patients were included only if they stay at least seven days in ICU. Some patients did not reach this period of time (discharge or death). This could involve a selection bias. However, during the study period, we did not notice a significant loss of patients due this reason.

To sum up, our study shows an association between an early supply of calories and proteins (within the first 24 hours) and

reduced ICU mortality. The energy goal of critically ill patients may be lower than the currently administered dose (25-30 kcal/kg/day) and those efforts to achieve this goal might not be justified, once critically ill patients, especially those who underwent surgery, show some degree of digestive tract dysfunction that put them at risk of serious complications when undergoing more aggressive protocols of energy repletion. The strategy of an early and limited amount of calories (not necessarily trophic nutrition) seems to be associated with a better outcome. Prospective studies evaluating and comparing these strategies are recommended.

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