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ORIGINAL

Nitrogen balance in mechanically ventilated obese patients

Balanço nitrogenado em pacientes obesos em ventilação mecânica invasiva

Raquel Stocker PÉRSICO[1] 0000-0003-0429-4504
Gabriela Corrêa SOUZA[2] 0000-0002-3620-4334
Oellen Stuani FRANZOSI[3] 0000-0002-5617-462X
Bibiana de Almeida Rubin ROVATI[3] 0000-0003-2911-5998
Zilda Elisabeth de Albuquerque SANTOS[2] 0000-0002-0007-0557

A B S T R A C T

Objective

This study aimed to evaluate if the protein intake recommendations for obese critically ill requiring mechanical ventilation are sufficient to promote a positive or neutral nitrogen balance.

Methods

Cross-sectional study that included 25 obese, ≥18 years old, undergoing mechanical ventilation and who were target to receive high-protein enteral nutrition therapy (2.0-2.5g/kg ideal body weight). Clinical, nutritional and biochemical variables were analyzed. Nitrogen balance was performed when patient was receiving full enteral nutrition therapy and was classified: positive when intake was greater than excretion; negative when excretion was greater than intake; neutral when both were equal.

Results

The characteristics of patients evaluated were 64.1±9.4 years old, clinical treatment 88%, body mass index 36.5±5.1kg/m², nitrogen balance 0.3g/day (-5.3 to 4.8g/day), protein intake 2.1g/day (2.0-2.3g/kg) ideal body weight. Of individuals analyzed, 52% showed positive or neutral nitrogen balance with median of 4.23g/day 2.41 to 6.40g/day) in comparison

[1] Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Ciências Médicas: Endocrinologia. R. Ramiro Barcelos, n. 2400, Santa Cecília, 90035-003, Porto Alegre, RS, Brasil. Correspondence to: ZEA SANTOS. E-mail: <zesantos@hcpa.edu.br>.

[2] Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Departamento de Nutrição. Porto Alegre, RS, Brasil.

[3] Hospital de Clínicas de Porto Alegre, Serviço de Nutrição e Dietética. Porto Alegre, RS, Brasil.

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to negative group with median of -5.27g/day (-10.38 to -3.86g/day). Adults had higher ratio of negative nitrogen balance (57.1%) than elderly (44.4%), with protein intake of 2.0 *versus* 2.1g/day, respectively. No correlation was found between nitrogen balance and variables assessed.

Conclusion

High-protein enteral nutrition therapy contributed to positive or neutral nitrogen balance for approximately half of obese ventilated individuals. With similar protein intake, elderly showed a higher proportion of positive or neutral nitrogen balance. Nitrogen balance can be influenced by various factors, so further studies are required to identify different protein needs in obese critically.

Keywords: Critical care. Enteral nutrition. Intensive care units. Mechanical ventilation. Nutrition therapy. Obesity.

RESUMO

Objetivo

Avaliar se as recomendações de ingestão proteica para obesos em ventilação mecânica invasiva são suficientes para promover balanço nitrogenado positivo ou em equilíbrio.

Métodos

Estudo transversal que analisou 25 obesos adultos, em ventilação mecânica invasiva e submetidos à terapia nutricional enteral hiperproteica (2,0-2,5g/kg de peso ideal). Variáveis clínicas, nutricionais e bioquímicas foram analisadas. O balanço nitrogenado foi realizado após a oferta plena da nutrição enteral e classificado como: positivo quando ingestão maior que excreção; negativo quando excreção maior que ingestão; neutro quando ambas foram iguais.

Resultados

As características dos pacientes avaliados foram idade 64,1±9,4 anos, índice de massa corporal 36,5±5,1kg/m², tratamento clínico 88%, balanço nitrogenado 0,3g/dia (-5,3 a 4,8g/dia), ingestão proteica 2,1g/dia (2,0-2,3g/kg) de peso ideal. Dos indivíduos analisados, 52% apresentaram balanço nitrogenado positivo ou neutro com mediana de 4,23g/dia (2,41 a 6,40g/dia), comparado ao grupo com balanço negativo -5,27g/dia (-10,38 a -3,86g/dia). Adultos apresentaram maior proporção de balanço nitrogenado negativo (57,1%) do que idosos (44,4%), respectivamente, com ingestão proteica semelhante de 2,0 versus *2,1g/dia. Não foi observada correlação entre balanço nitrogenado e variáveis analisadas.*

Conclusão

A terapia nutricional enteral hiperproteica promoveu um balanço nitrogenado positivo ou neutro em cerca de metade dos obesos em ventilação mecânica invasiva. Com ingestão proteica semelhante, idosos apresentaram maior proporção de balanço positivo ou neutro do que adultos. O balanço nitrogenado pode ser influenciado por diversos fatores e por esse motivo mais estudos são necessários para identificar diferentes necessidades proteicas em pacientes obesos críticos.

Palavras-chave: *Cuidados críticos. Nutrição enteral. Unidades de terapia intensiva. Ventilação mecânica. Terapia nutricional. Obesidade.*

INTRODUCTION

In the critical care setting, obesity can contribute to exacerbate ventilatory, cardiovascular, renal and endocrine dysfunctions and pharmacokinetic and pharmacodynamic alterations, leading to an increased metabolic and inflammatory state [1-4]. Due to these metabolic alterations added to physical inactivity, muscle protein synthesis is decreased and muscle mass can be utilized as an energy substrate for gluconeogenesis, leading to excessive proteolysis, a condition associated with higher mortality [3-6].

Nutritional Therapy (NT) recommendations suggest hypocaloric high-protein NT for obese, with the purpose to prevent overfeeding, promote an adequate glycemic control and a positive or neutral Nitrogen Balance (NB), in order to contribute to immune function regulation, wound healing and to decrease the loss of muscle mass [6-12].

Studies suggest that high-protein NT contributes to an adequate NB in obese individuals even when in a hypocaloric diet [13-17]. However, these studies were based on small sample sizes, heterogeneous populations, with most individuals categorized as surgical or trauma patients, most of whom received parenteral nutrition, instead of Enteral Nutrition (EN) and were not necessarily submitted to Mechanical Ventilation (MV) [7,9]. Considering the characteristics of these studies, there are concerns regarding the generalization of the recommendations to all obese individuals admitted to Intensive Care Units (ICU), including those on MV. The objective of this study is to evaluate if the protein intake recommendations for obese critically ill requiring MV and with hypocaloric EN are sufficient to promote a positive or neutral NB.

METHODS

Cross-sectional study conducted at the adult ICU of a public teaching hospital. The sample was composed by patients classified as obese according to Body Mass Index (BMI) ≥30kg/m², ≥18 years old, on MV and receiving full EN. Between April and August 2018, 70 patients underwent the screening assessment, and after exclusions (n=45), 25 individuals were included on this study. Exclusion criteria were the presence of diarrhea, renal failure (considered as serum creatinine >2.0mg/dL, glomerular filtration rate <30mL/min or renal replacement therapy), hepatic failure (considered as bilirubin levels higher than three times the reference value) and pregnancy.

The following data were analyzed: (a) socio-demographic: age, gender, ethnicity; (b) clinical: diagnosis at admission classified as clinical (respiratory, neurological, cardiovascular or gastrointestinal) or surgical, comorbidities, disease severity (SAPS 3 score – Simplified Acute Physiology Score III and SOFA score – Sequential Organ Failure Assessment Score) (c) nutritional: body weight, height, BMI, time until the onset of NT, protein and caloric intake and adequacy; (d) biochemical: one time 24-hour urinary urea excretion; (e) outcomes: NB, MV time, ICU and hospital time and mortality in the ICU and in the hospital.

Anthropometric data was collected by the staff at the moment of admission, height was measured using a Luft® ruler [18], and weight by using a Hill Rom® in-bed. Subsequently, BMI was calculated and patients were considered class I obesity when BMI ≥30kg/m², class II when BMI ≥35kg/m² and class III when BMI ≥40kg/m². There were no changes in the routine of care at the unit.

Nutritional therapy protocol utilized stratifies the protein recommendations by BMI degrees [7]. The protein target for BMI 30 to 40kg/m² is 2.0g/kg of Ideal Body Weight (IBW) and for BMI >40kg/m² is 2.5g/kg IBW, and calorie target for BMI 30 to 50kg/m² is 11-14Kcal/kg of Actual Body Weight (ABW) and for BMI >50kg/m² is 22-25Kcal/kg IBW [7]. After defining individual calorie and protein targets, the amount of EN formula is calculated and when protein targets are not reached with enteral formulas, protein supplements are prescribed.

Nutritional therapy was provided by enteral route, using a high-protein polymeric fiber-free formula, with caloric density of 1.5kcal/mL. During the first 48 hours in ICU, patients were evaluated by ICU physicians regarding to hemodynamic and perfusion conditions to start NT. Beggining of EN was at 10 to 30mL/hour and it was increased in 10 to 15mL/hour per day until the target is reached. After EN target was reached, protein supplements were included. Protein supplements were constituted by 100% hydrolyzed whey protein and provided 10-20 grams-dose, given 3 to 5 times a day, as targets prior determined. At the unit, the diet is provided continuously, using a closed system, with nutritional targets computed for 22 hours of feeding, considering a 2-hour break every day for ICU procedures aiming to optimize nutritional adequacy.

Nitrogen Balance was measured one day after the patient achieved the prescribed nutritional target, and was calculated by the equation:

NB (g/day)=nitrogen intake (g/day) – [urinary urea nitrogen (g/day)+4 (g/day)].

Considering 4g as a constant factor from integumentary, gastrointestinal and insensible losses [19]. NB was defined as positive when nitrogen intake was greater than excretion, negative when excretion was greater than intake and in equilibrium or neutral when both were equal. Nitrogen intake was computed using records from the total amount of enteral diet and protein supplements received during the NB realization day. Urinary urea nitrogen was measured in a one-time 24-hour urine sample, being the urine collected by a urinary catheter every six hours and stored in a refrigerator during the 24 hours of collection. This study only included patients that already had a urinary catheter for clinical purposes. The urine analyses were realized in the clinical analyses laboratory of the hospital using the glutamate dehydrogenase enzymatic kinetic assay method. Electronic medical records were analyzed to assess clinical, demographic, nutritional and biochemical data. The patients were included only after the informed consent was obtained from those legally responsible. This study was approved by the Institutional Ethics Committee under record number #18-0006.

The study conducted by Dickerson *et al*. [15] was used to estimate the sample size, considering the mean and standard deviation of daily protein ingestion of 2.3±0.2g/kg IBW, a standard error of 0.2, 95% confidence interval and 10% of losses, requiring 25 patients for inclusion. SPSS, v.21.0 (IBM® SPSS® Statistics Inc., Chicago, Illinois, United States) was used for statistical analysis with a statistically significant *p* value of <0.05. Mann-Whitney test was performed for comparisons between continuous variables. Correlation analysis between socio-demographic, clinical and nutritional variables and NB were conducted with Spearman's rank correlation. Fisher's exact test was used to association analysis between nutritional variables and outcomes.

RESULTS

All included patients were ventilated obese, of which 18 (72%) were 60 years or older, 22 (88%) were in ICU for clinical treatment and three (12%) for surgical treatment and were predominantly female and white. Eleven (44%) patients had class I obesity, nine (36%) class II, while five (20%) had class III obesity. All individuals received EN and 22 (88%) received early EN, with onset in up to 48 hours after admission in ICU. Calorie and protein adequacy were higher than 95% for 21 (84%) and 22 (88%) individuals, respectively. Calorie intake was 16 (15-17) kcal/kg ABW, data calculated for 24 (96%) patients because one individual had BMI >50kg/m². Median protein ingestion was 2.1g/kg (2.0-2.3g/kg) IBW. Table 1 describes socio-demographic, clinical and nutritional characteristics of participants.

Median overall NB was 0.3g/kg (-5.3 to 4.8g/day), with median time for NB measurement of three (2-6) days after ICU admission, the period required for NT to reach the target. Considering clinical outcomes, median length of MV was 10 (7-19) days, ICU was 14 (8-23) days and hospital was 28 (19-49) days. Mortality rates in ICU and hospital were of 20% and 32%, respectively.

Thirteen (52%) individuals had positive or neutral NB, while twelve (48%) had negative NB. Table 2 describes comparisons between NB groups. Differences between NB groups for NB and urinary urea excretion were observed. Similar protein intake, age, BMI and SAPS and no differences for secondary outcomes (MV days, ICU and hospital time, mortality in ICU and in hospital) were found.

When stratified by age, negative NB was observed in 44.4% of elderly (≥60 years old) and 57.1% of adults, without statistical difference. The median NB for elderly and adults were 0.7g/kg (-6.4 to 4.5g/kg) *versus* -3.5g/kg (-4.7 to 5.9g/day) and median protein intakes were 2.1g/kg (2.0-2.3g/kg) *versus* 2.0g/kg (1.9-2.2g/kg) IBW, respectively.

Table 1 – Socio-demographic, clinical and nutritional characteristics. *Hospital de Clínicas de Porto Alegre*, Brazil, 2018.

Characteristics	Number (%)	M±SD	Median (P25-75)
Age, years		64.1±9.4	
Gender, female	22 (88)		
Ethnicity, white	19 (76)		
Diagnosis at admission			
Respiratory	9 (36)		
Neurological	8 (32)		
Cardiovascular	3 (12)		
Gastrointestinal	2 (8)		
Surgical	3 (12)		
Oncologic	2 (8)		
Abdominal Aortic Aneurism	1 (4)		
Comorbidities			
Hypertension	16 (64)		
Diabetes	11 (44)		
COPD	5 (20)		
Neoplasia	3 (12)		
Others	20 (80)		
Body weight, kg			86.2 (79.7-102.0)
BMI, kg/m²		36.5±5.1	
Calorie adequacy, %			104.0 (97-106)
Protein adequacy, %			102.0 (98-103)
Non-protein calorie/gN2 ratio			49.0 (47-55)
SAPS 3, points		66.4±12.4	
SOFA, points		2.7±0.8	

Note: Values expressed as number (%), M±SD or median (P25-75). BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; gN2: Grams of nitrogen; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment Score; M: Mean; SD: Standard Deviation.

Table 2 – Comparisons according to nitrogen balance groups. *Hospital de Clínicas de Porto Alegre*, Brazil, 2018.

Characteristics	Positive NB (n=13)*		Negative NB (n=12)		*p*
	M±SD	Median (P25-75)	M±SD	Median (P25-75)	
NB, g/d		4.23 (2.41; 6.40)		-5.27 (-10.38; -3.86)	<0.001
Age, years	65.1±10.3		63.1±8.7		NS
BMI, kg/m²	37.1±6.1		35.8±3.7		NS
Protein intake, g/kg IBW	2.09±0.31		2.07±0.22		NS
Urinary urea excretion, g/d	24.7±10.9		46.8±13		<0.001
SAPS 3, points	64.5±12.8		68.4±12.2		NS
MV, d		10 (7.5; 23)		10 (5.5; 18)	NS
ICU stay, d		14 (9; 26)		13.5 (8.3; 24.3)	NS
Hospital stay, d		30 (20; 50)		27 (18.3; 47.5)	NS

Note: *Positive or Neutral NB. Values expressed as M±SD or median (P25-75). BMI: Body Mass Index; IBW: Ideal Body Weight; ICU: Intensive Care Unit; MV: Mechanical Ventilation; NB: Nitrogen Balance; NS: Non-significant; SAPS: Simplified Acute Physiology Score; M: Mean; SD: Standard Deviation.

Patients with class III obesity showed a higher prevalence of positive or neutral NB, being 60.0% compared to class I with 54.5%, and class II with 44.4%. The median of NB in these groups was 1.66g/day (-5.88 to 3.24g/day) for class I, -1.81g/day (-6.19 to 4.64g/day) for class II, and 4.23g/day (-5.93 to 7.22g/day) for class III obesity, without statistical difference.

No significant correlation was found between NB and socio-demographic, clinical and nutritional characteristics, as seen in Table 3. No association was found between NB and mortality in ICU and in hospital.

Table 3 – Correlation between nitrogen balance and associate variables[a]. *Hospital de Clínicas de Porto Alegre*, Brazil, 2018.

Characteristics	r-value	*p*-value
Age, years	-0.005	NS
BMI, kg/m²	0.237	NS
Protein intake, g/d	0.163	NS
Non-protein calorie/gN2	0.240	NS
SAPS 3, points	-0.194	NS
SOFA, points	0.028	NS
MV, d	0.176	NS
ICU stay, d	0.147	NS
Hospital stay, d	-0.104	NS

Note: [a]Spearman's Rank Correlation. n=25 BMI: Body Mass Index; ICU: Intensive Care Unit; MV: Mechanical Ventilation; NS: Non-significant; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment Score.

DISCUSSION

All individuals received high-protein enteral feeding, with a median of 2.1g/kg IBW, providing positive or neutral NB for approximately half of obese individuals requiring MV. Analyzing by groups, positive or neutral *versus* negative NB, a difference was found for NB and urinary urea excretion, but no differences were found for protein and calorie intake and adequacy, and SAPS 3 score. No significant correlation was found between NB and assessed variables. No association was found between NB and the outcomes assessed, and we hypothesize that it could be explained by the restricted number of patients in our sample and maybe due to its heterogeneity. Patients had different obesity degrees and diagnoses at admission, also, even the most of them were admitted for clinical purposes, three were surgical and three had oncologic disease, situations that can influence the protein needs.

Catabolism is exacerbated by critical illness, specially protein catabolism that contributes to loss of muscle mass, with loss proportional to disease severity [20]. Considering that stressed obese commonly are insulin resistant, this group may have a higher protein turnover and greater catabolism [21]. Some studies showed that a greater adequacy in protein and calorie targets is associated with greater outcomes for ICU patients, as reported by Nicolo *et al*. [22], where a protein adequacy >80% independent of calorie intake had association with reduced mortality rates. In our study, protein adequacy was greater than 95% for most of the sample, but even while receiving adequate protein intake no difference was found between positive and negative NB groups in relation to mortality rate.

Recommendations suggest that obese ICU patients can achieve adequate NB receiving high-protein NT, even when receiving hypocaloric diet [7]. However, these studies were conducted with populations of obese who were mostly classified on admission in ICU as surgical or trauma, and who were predominantly administered parenteral nutrition, with no difference in NB values found when compared to patients who received hypocaloric *versus* eucaloric high-protein NT [13,23,24].

Recently studies demonstrated that hypocaloric high-protein NT is safe to obese critically ill, including sarcopenic obese [6,11,21,25]. A subset analysis of pre-morbid obese critically ill found that individuals with hypocaloric *vs* normocaloric NT, but with similar protein intake, had no statistical difference in relation to ICU and hospital time, mortality and infection rates [26].

In our sample 52% had positive or neutral NB, being NB 0.3 (-5.3 to 4.8) g/day, with median protein intake of 2.1g/kg IBW receiving enteral feeding. A study with 25 mechanically ventilated obese patients found a NB of -2.3±5.1g/day, but protein requirements met 25% of target [17]. Forty obese critically ill subjects receiving hypocaloric *versus* eucaloric EN, with 1.58-1.99g/kg IBW of protein, found NB close to neutral, though all NB had negative values in the first two weeks of stay at ICU [14]. However, obese critically ill with traumatic injury showed similar results to our study in relation to positive or neutral NB, being 55% and 56% for older and younger individuals, respectively [15,16]. In some specific situations, critically ill obese may need higher amounts of protein compared to nonobese, as described in two studies that evaluated patients in extracorporeal membrane oxygenation, whereas obese groups had a more pronounced negative NB [27,28].

Literature suggests that elderly individuals may have a decline in anabolic response and difficulty mobilizing body fat stores as energy sources, conditions that lead to an increase consumption of muscle mass [11,29]. Our analysis showed that adults had higher rates of negative NB compared to elderly subjects. In a similar way, a study that compared elderly obese patients to adult ones, showed that adults had greater values for NB 3.44 *versus* 0.2g/day, with similar protein ingestion of 1.6-1.7g/kg adjusted body weight [29]. However Dickerson et al showed that in trauma patients NB values were lower, but not statistically significant, between adults (-4.9d/day) in comparison to elderly (-3.2g/day) with similar protein intake of 2.3g/kg IBW of protein [15].

Nitrogen balance may be influenced by various factors and it has the aim to help in evaluation of protein intake adequacy to individual's needs. Although our sample consisted solely by obese patients undergoing MV, this study has some limitations. NB was measured only once, at the early stage of acute injury and sample was not stratified by severity, thus our results may reflect various metabolic states, making it difficult to interpret protein requirements and adequacy at different disease severities and stages. NB was not analyzed according to different degrees of obesity and number of comorbidities, which can influence in protein needs.

CONCLUSION

Our data suggest that a daily protein intake around 2.1g/kg IBW was able to promote positive or neutral NB in 52% of the population of obese individuals undergoing MV, enteral NT and predominantly receiving clinical treatment. Studies with large sample size, serial NB measures in the first ICU week, severity stratification, and analysis according to different obesity degrees are required in order to identify different protein needs of obese critically ill patients undergoing MV.

CONTRIBUTORS

All authors have contributed to the conception, design, analysis and interpretation of the data and agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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