Natália Sanchez Oliveira[1],
Lúcia Caruso[2], Denise Pimentel
Bergamaschi[3], Flávia de Conti
Cartolano[4], Francisco Garcia
Soriano[2]

Impact of the adequacy of energy intake on intensive care unit mortality in patients receiving enteral nutrition

Impacto da adequação da oferta energética sobre a mortalidade em pacientes de UTI recebendo nutrição enteral

1. Hospital Nutrition Training Program – Hospital Universitário, Universidade de São Paulo – USP – São Paulo (SP), Brazil. (2009)
2. Adult Intensive Care Unit – Hospital Universitário, Universidade de São Paulo – USP – São Paulo (SP), Brazil.
3 Department of Epidemiology, Faculdade de Saúde Pública, Universidade de São Paulo – USP – São Paulo (SP), Brazil.
4. Hospital Nutrition Training Program – Hospital Universitário Universidade de São Paulo – USP – São Paulo (SP), Brazil. (2008)

This study was conducted at the Hospital Universitário – Universidade de São Paulo – USP – São Paulo (SP), Brazil.

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Corresponding author:
Lucia Caruso
Av. Professor Lineu Prestes, 2565 - Cidade Universitária – 1º A
Zip Code: 05508-900 - São Paulo (SP), Brazil.
Phone/Fax: +55 (11) 3039-9357
E-mail: snd@hu.usp.br

ABSTRACT

Objective: To investigate the relationship between adequacy of energy intake and intensive care unit mortality in patients receiving exclusive enteral nutrition therapy.

Methods: Observational and prospective study conducted during 2008 and 2009. Patients above 18 years with exclusive enteral nutrition therapy for at least 72 hours were included. The adequacy of energy intake was estimated by the administered/prescribed ratio. Non-conditional logistic regression was used to assess the relationship between predictive variables (adequacy of energy intake, APACHE II, gender, age, and intensive care unit length of stay) and intensive care unit mortality.

Results: Sixty-three patients (mean 58 years, 27% mortality) were included, 47.6% of whom received more than 90% of the energy prescribed (mean adequacy 88.2%). Mean energy balance was -190 kcal/day. Significant associations between death in the intensive care unit and the variables age and intensive care unit length of stay were observed, after removing the variables adequacy of energy intake, APACHE II, gender and age during the modeling process.

Conclusion: In our study, adequacy of energy intake did not affect intensive care unit mortality. Carefully followed enteral nutrition protocols, resulting in an administered/prescribed ratio above 70%, are apparently not sufficient to impact the mortality rates in the intensive care unit. Therefore, it may not be necessary to achieve 100% of the targeted energy, considering the high frequency of enteral feeding interruptions due to gastrointestinal intolerance and fasting for tests and procedures. Additional research is needed to identify the optimal energy intake for improved outcomes and reduced costs.

Keywords: Enteral nutrition; Energy requirements; Measures of association, exposure, risk or outcome; Intensive care units; Mortality

INTRODUCTION

Intensive care unit (ICU) patients can have issues such as metabolic stress, catabolism, prolonged immobilization and inappropriate nutrition intake, any of which may result in negative energy balance, meaning that the expended energy overcomes the intake.[1,2]

Observational trials have shown an association between negative energy balance and an increased rate of complications (especially those related to infection) as well as a prolonged ICU stay.[3-5]

Adequacy of energy intake for critically ill patients poses a significant

challenge. Enteral nutrition therapy (ENT), the first option when oral feeding is not feasible, frequently results in insufficient energy intake, as many factors may cause interruptions of the enteral formula administration, such as gastrointestinal intolerance (abdominal distension, vomiting, diarrhea) and fasting for tests and procedures.[6]

In clinical practice, the intake of ENT patients is likely to be below the prescription targets, which are based on estimated nutrition needs.[7,8]

Additionally, the literature is controversial regarding the optimal amount of energy to be provided for ICU patients. Some authors debate whether all of the considerable efforts to achieve 100% of the prescription target would effectively result in clinically relevant improved outcomes.[9]

In a study by Krishnan et al.,[10] patients in the highest energy tercile, receiving ≥ 66% of the prescribed energy, were less likely to be discharged from the hospital and discharged from the ICU with spontaneous breathing than were patients in the lowest tercile (receiving 0 to 32% of the prescribed energy). In addition, patients in the middle tercile, receiving 33 to 65% of the prescribed energy, were more likely to be weaned from the ventilator before discharge from the ICU than those in the lowest tercile. This suggests a therapeutic window above which energy intake would not provide additional benefit and, conversely, could be related to poorer outcomes.

Faisy et al.[11] in a study conducted in prolonged mechanical ventilation ICU patients, found significantly higher mortality in patients in the higher energy deficit quartile. Using multivariate analysis, the mean energy deficit was found to be independently associated with ICU mortality. Therefore, the authors reiterated that energy intake as close as possible to the prescribed estimates can provide better ICU outcomes.

This lack of a consensus in the medical literature motivated the present study, which was conducted to investigate the relationship between adequacy of energy intake and ICU mortality in exclusive ENT patients.

METHODS

This was an observational prospective study conducted in the adult ICU of the Hospital Universitário da Universidade de São Paulo, Brazil, collecting data during the second semesters of 2008 and 2009. Patients above 18 years old receiving exclusive ENT for at least 72 hours were included. The exclusion criteria were non-consenting patients and patients receiving palliative care.

The energy estimation (kcal) was provided for each clinical condition according to an existing protocol,[12] using an energy per body weight (kcal/kg) calculation for sepsis and renal or liver failure and the Harris & Benedict formula for other conditions. For calculation purposes, the usual body weight, either adjusted or ideal, was obtained from reference tables that included age range[13,14] and height (cm), which was either reported or estimated based on the knee dimension using the Chumlea et al. equations for adult[15] and elderly patients.[16]

Post-pyloric tubes were installed, with radiographic confirmation. The enteral formulas were administered continuously via infusion pumps for approximately 22 hours daily, with estimated 2-hour breaks for medication.

The progression of the infusion speed complied with the protocol,[17] beginning at 25 mL/hour and increasing by 10 mL/hour every 4 hours until reaching an initial target of 55 mL/hour. Next, each patient progressed to an individual target, using one of the available enteral formulas: normocaloric and normoproteic, normocaloric and hyperproteic, or hypercaloric and hyperproteic. No formula contained immunonutrients.

Data on gender, age, weight, height, diagnosis and Acute Physiology and Chronic Health Evaluation (APACHE II)[18] prognosis score were recorded upon admission to the ICU. The infused volume within the preceding 24 hours was recorded daily according to the nursing chart. Recording of nutrition diet data started with the ENT introduction and stopped upon ICU discharge, death or initiation of an alternative modality of nutrition.

The energy balance was calculated as the difference between the energy intake (from the infused volume records) and estimated energy requirements. The adequacy of energy intake was estimated as the ratio between the calculated and prescribed values and the prescribed and administered values.

The results are shown as the mean and standard deviation for numerical variables, number (n) or percentage (%) for categorical variables, including the 95% confidence interval (CI) estimated for binomial distribution. The variables were compared using Student's *t* test and the 95% confidence interval.

The relationship between predictive variables and the ICU mortality outcome was investigated using a non-conditional logistic regression model. It began with the complete model and consecutively excluded variables using a likelihood ratio test.[19,20]

The modeling began with the following variables: percent adequacy of the energy intake (<70%; 70-90%; >90%); APACHE II (<15; 15-23; >23); gender (male; female); age (< 60 years; ≥ 60 years) and length of ICU stay (<14 days; ≥14 days).

Statistical decisions were based on the descriptive test value (p value). The statistical analysis was performed using the Epi Info version 3.5.1 and Stata version 9.0 software. The study was approved by the ethics committee of the institution (CEP 603/05), contingent upon the signature on an informed consent form of the subject or the subject's legal representative.

RESULTS

During the study, 87 adult patients admitted to the ICU received exclusive ENT, and 23 of them failed to comply with the inclusion criteria (22 patients were under palliative care; 1 refused consent). One patient, who presented an outlier value for time of ICU stay, was excluded from the regression analysis.

Data from 63 patients were analyzed. Mean age was 58 years, gender distributions were similar (51% female), and the mean APACHE II score was 19.5. The main ICU admission diagnoses were respiratory disorders (37%), followed by heart disorders (17%) and sepsis (16%). The mortality rate was 27%. Regarding appropriate energy intake, 7.9% of the patients received less than 70% of the prescribed energy, 44.4% received between 70 and 90%, and 47.6% received above 90% of the prescribed energy (Table 1).

Table 2 shows the mean calculated, prescribed and administered energy values and the energy balance. Mean percent adequacy between prescribed and calculated energy was 100.5% and between administered and prescribed energy, 88.2%. The mean administered/calculated energy ratio was 88.7%. This is reflected in the mean energy balance, which was slightly negative (less than 190 kcal/day).

Fifty-four (86%) of the patients had negative mean energy balances; their deficits ranged between -690.9 and -4.6 kcal/day. The remaining patients (14%) had positive mean energy balances, with excesses between 2.8 and 224.3 kcal/day.

Table 1 – Population characteristics (N=63)

Characteristics	Result
Age (years)	58.0 ± 20
Male (N=31)	49
Female (N=32)	51
APACHE II	19,5 ± 5,8
ICU admission diagnosis	
Respiratory (N=23)	37
Sepsis (N=10)	16
Neurologic (N=3)	5
Cardiologic (N=11)	17
Trauma (N=1)	2
Liver diseases (N=3)	5
Surgeries (N=6)	10
Mixed shock (N=2)	3
Other (N=4)	6
Length of ICU stay (days)	15.3 ± 10.8
Time to ENT initiation (hours)	28.8 ± 21.1
Length of ENT (days)	12.8 ± 9.4
Adequacy of energy intake*	
Below 70%	7.9
Between 70 and 90%	44.4
Above 90%	47.6
Mortality rate (N=17)	27.0
	(95%CI: 16.6 – 39.7)

Source: Adult ICU, HU-USP, 2008-2009. APACHE II - Acute Physiology and Chronic Health Evaluation; UTI – intensive care unit; 95%CI – 95% confidence interval; *administered over prescribed energy. Results expressed as percent or mean ± standard deviation.

Table 2 – Energy values: calculated, prescribed, administered; and energy balance (kcal/day) (N=63)

Energy	Mean (standard deviation)	Minimum	Maximum
Calculated	1587.6 (224.8)	680.0	2017.0
Prescribed	1592.5 (217.5)	770.0	1980.0
Administered	1406.9 (292.2)	624.9	2009.5
Energy balance	- 190.3 (213.3)	- 690.9	224.3

Source: Adult ICU, HU-USP, 2008-2009. Results expressed as mean ± standard deviation.

Patients with a fatal outcome had significantly higher mean age and APACHE II score than did survivors (p<0.001 and p=0.007, respectively). No statistically significant difference was found regarding gender, ICU time of stay, fasting time before ENT initiation and ENT days (Table 3).

When the groups are analyzed for the percentage of energy intake adequacy (<70%, 70-90%, >90%), no statistically significant difference was found for age

Table 3 – Comparison of characteristics of patients who died (N=17) and those who survived (N=46)

Characteristics	Survivors (N=46)	Deceased (N=17)	p value
Mean age (years)	53 ± 19	72 ± 13 *	<0.001
Male/Female	46 (N=21) / 54% (N=25)	59 (N=10) / 41 (N=7)	0.317
APACHE II	18.3 ± 5.6	22.6 ± 5.3*	0.007
ICU length of stay (days)	13.6 ± 7.5	19.9 ± 16.2	0.139
Time before ENT (hours)	27.0 ± 19.1	33.9 ± 26.2	0.345
Length of ENT (days)	11.3 ± 6.9	16.7 ± 13.7	0.140
Diagnosis			
Respiratory	35 (N=16)	41 (N=7)	
Sepsis	15 (N=7)	18 (N=3)	
Neurologic	7 (N=3)	0* (N=0)	
Cardiologic	20 (N=9)	12 (N=2)	
Trauma	2 (N=1)	0* (N=0)	
Liver disease	7 (N=3)	0* (N=0)	
Surgery	7 (N=3)	12 (N=2)	
Mixed shock	0 (N=0)	12* (N=2)	
Other	9 (N=4)	6 (N=1)	
Mean energy balance (kcal/day)	- 168.08 ± 200.17	- 250.29 ± 241.52	0.222
Adequacy of energy intake*			
Lower than 70%	6.5	11.8	0.183
Between 70 and 90%	39.1	58.8	
Above 90%	54.4	29.4	

Source: Adult ICU, HU-USP, 2008-2009. APACHE II - Acute Physiology and Chronic Health Evaluation; ICU – intensive care unit; ENT - enteral nutrition therapy. Results expressed as mean (standard deviation) or percent (%); * statistically significant difference (p<0.05 or lack of 95% confidence interval overlap); *Administered over prescribed energy. Results expressed as percent or mean ± standard deviation.

Table 4 – Final model for multivariate analysis of death in intensive care unit patients under exclusive enteral nutrition therapy

Variables	Adjusted OR	95%CI	Standard error	Z (Wald)	p value
Age	10.60	(1.86 – 60.30)	9.40	2.66	0.008
Length of ICU stay	10.75	(1.76 – 65.56)	9.92	2.57	0.010

Source: Adult ICU, HU-USP, 2008-2009. OR - Odds Ratio; 95%CI – 95% confidence interval; ICU – intensive care unit.

(p=0.690), time of ICU stay (p=0.235) or APACHE II score (p=0.367).

For the final logistic regression model, a statistically significant difference was found for death and the explanatory variables, age and time of ICU stay (Table 4), after removing the variables of energy intake, APACHE II and gender during the modeling process.

DISCUSSION

In this study, the adequacy of energy intake for ICU adult patients under exclusive enteral nutrition had no influence on the mortality rate.

The consistency between administered and prescribed energy values in this ICU (88.2%) should be highlighted. In ICU patients with mechanical ventilation, Reid[21] found 81% of appropriate energy intake, while O'Meara et al.[8] reported only 50%.

The percentage of adequacy found here between prescribed and administered values reflects local practices: adherence to the enteral nutrition protocol that defines measures to achieve the nutrition target and to manage intercurrences, such as increased gastric residues, and endeavors by the Enteral Nutrition Multidisciplinary Team (ENMT) to minimize the fasting time caused by extubation and routine procedures.

The mean energy balance of -190 kcal/day was far below the average deficit of more than 1,200 kcal/day reported by Faisy et al.[11] A possible explanation for this difference is that Faisy's study, the diet prescription was not based on the estimated energy expenditure.

When diet is prescribed individually on the basis of energy requirements, as in our study, there is a trend toward lower energy deficits.

In a trial conducted by Villet et al.,[3] the mean energy balance was lower for the fourth week in the hospital (-625 kcal/day) than for the first week (-1,270 kcal/day). The delay before starting enteral nutrition in Villet's trial (mean 74.4 hours) contributed to the size of the energy deficit during the first week.

The mean time to start ENT in this study, 28.8 hours, is consistent with guidelines that recommend ENT initiation within the first 24 to 48 hours after admission.[22] Both early introduction and rapid attainment of the nutrition target may also have contributed to the lower energy deficit.

The results of the logistic regression analysis indicate that both age and length of ICU stay were factors associated with death in the studied population. The literature shows that advanced age is associated with increased hospital mortality in patients admitted to the ICU.[23,24] However, other studies suggest that age alone is not a strong ICU mortality predictor.[25-27]

The ICU length of stay was also identified as a mortality-associated factor in some trials. Marin et al.[28] observed significantly higher ICU mortality in patients who remained more than 21 days in the ICU (24%) when compared with patients who had shorter stays (11%). In a study by Abelha et al.[29] in a surgical ICU, an ICU of more than 3 days was identified as an independent ICU mortality-associated factor.

As could be anticipated, the mean APACHE II score was significantly higher in patients who died, as compared to survivors. Some results from the literature indicate that the APACHE II score is an independent ICU mortality-associated predictor.[30,31] However, in our regression model, as in the study by Bregeon et al.,[32] the APACHE II score did not independently predict ICU mortality.

Excessively hypercaloric or hypocaloric ENTs are not recommended in critically ill patients;[22] however, the ideal energy intake in relation to the prescribed amount remains to be found in the medical literature. International guidelines recommend that the energy intake is as close as possible to the established target, some investigators support what has been called permissive underfeeding.

The argument is justified by the fact that more aggressive nutrition support could cause hyperglycemia[33] and increase residual gastric volume, favoring aspiration.[34] Additionally, there is evidence that energy restriction may reduce oxidative stress, mitigate the inflammatory response and improve insulin sensitivity.[22,35]

Results from some observational studies support the claim that the ideal energy intake can be below the prescribed target, as intakes closer to the target have been associated with poorer outcomes, such as a prolonged ICU stay and reduced likelihood of ventilator weaning before discharge from the ICU.[9,10] However, one could argue that these results are biased because patients staying longer in an ICU are more likely to achieve the energy target and, in these patients, prolonged exposure to the ICU environment itself could increase the risk of complications that are not necessarily related to energy intake.

In the recent study by Arabi et al.,[35] an adjustment was made for the confounding variable ICU length of stay. They showed that energy intakes closer to the target (> 64.6%) were associated with significantly increased hospital mortality, duration of mechanic ventilation and risk of acquiring infections in the ICU. The ICU mortality was higher in patients receiving more than 64.6% of the prescribed energy (35%), as compared with those receiving between 33.4% and 64.6% (24%), and also higher, although not statistically significant, for patients receiving less than 33.4% of the prescribed energy (21%) (p=0.08).

Of note, the mean adequacy between administered and prescribed energy found by Arabi et al. was 50%, and only one-third of the patients had less than 65% of the calculated target.[35] Additional studies are necessary to determine whether reducing energy intake may improve the outcome of ICU patients.

Conversely, a multicenter observational study including 2,772 mechanically ventilated patients[36] showed that a 1,000 kcal/day increase was associated with significantly reduced mortality. The patients who achieved more benefits were those with body mass indexes below 25 or above 35 kg/m^2.

Evidence from clinical trials and meta analysis apparently confirms the hypothesis that higher ENT intakes are associated with improved outcomes, especially when early-initiated ENT is compared with delayed ENT,[37] and provided that an individual and careful calculation of energy and protein requirements is established. However, the association between 100% achievement of the prescribed energy and clinically relevant outcomes is unclear.

Therefore, one could review the ENMT endeavor to ensure that the full prescribed diet is administered,

considering the frequent interruptions of enteral nutrition in ICU, fasting for tests, routine procedures and gastrointestinal intolerance issues.

The data from this study suggest that achieving administration of at least 70% of the prescribed amount could be an appropriate target that is easier to achieve in clinical practice. The sample size and the observational character of the study are limitations to any generalization of our conclusions. Clinical trials that investigate the optimal administered/prescribed ratio in ICU patients under enteral nutrition therapy are necessary to address the goals of reducing ICU length of stay, complications and mortality.

CONCLUSION

Adequacy of energy intake in exclusive ENT patients had no influence on the mortality rate of ICU patients. The logistic regression analysis indicated that age and length of ICU stay are mortality-related factors. Careful adherence to enteral nutrition protocols with rates above 70% of the calculated requirements for ICU patients from 2 up to 3 weeks apparently had no effects on mortality. Therefore, the benefit of levels near 100% should be examined. Future research is required to identify the optimal energy intake targets that could result in significant reductions of complications, mortality and costs.

RESUMO

Objetivo: Investigar a relação entre adequação da oferta energética e mortalidade na unidade de terapia intensiva em pacientes sob terapia nutricional enteral exclusiva.

Métodos: Estudo observacional prospectivo conduzido em uma unidade de terapia intensiva em 2008 e 2009. Foram incluídos pacientes >18 anos que receberam terapia nutricional enteral por >72h. A adequação da oferta de energia foi estimada pela razão administrado/prescrito. Para a investigação da relação entre variáveis preditoras (adequação da oferta energética, escore APACHE II, sexo, idade e tempo de permanência na unidade de terapia intensiva e o desfecho mortalidade na unidade de terapia intensiva, utilizou-se o modelo de regressão logística não condicional.

Resultados: Foram incluídos 63 pacientes (média 58 anos, mortalidade 27%), 47,6% dos quais receberam mais de 90% da energia prescrita (adequação média 88,2%). O balanço energético médio foi de -190 kcal/dia. Observou-se associação significativa entre ocorrência de óbito e as variáveis idade e tempo de permanência na unidade de terapia intensiva, após a retirada das variáveis adequação da oferta energética, APACHE II e sexo durante o processo de modelagem.

Conclusão: A adequação da oferta energética não influenciou a taxa de mortalidade na unidade de terapia intensiva. Protocolos de infusão de nutrição enteral seguidos criteriosamente, com adequação administrado/prescrito acima de 70%, parecem ser suficientes para não interferirem na mortalidade. Dessa forma, pode-se questionar a obrigatoriedade de atingir índices próximos a 100%, considerando a elevada frequência com que ocorrem interrupções no fornecimento de dieta enteral devido a intolerância gastrointestinal e jejuns para exames e procedimentos. Pesquisas futuras poderão identificar a meta ideal de adequação da oferta energética que resulte em redução significativa de complicações, mortalidade e custos.

Descritores: Nutrição enteral; Necessidade energetic; Medidas de associação, exposição, risco ou desfecho; Unidades de terapia intensiva; Mortalidade

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