The effect of L-alanyl-L-glutamine dipeptide supplemented total parenteral nutrition on infectious morbidity and insulin sensitivity in critically ill patients*

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Objective: **The aim of this study was to assess the clinical efficacy of alanine-glutamine dipeptide-supplemented total parenteral nutrition defined by the occurrence of nosocomial infections. Secondary parameters included Sequential Organ Failure Assessment score, hyperglycemia and insulin needs, intensive care unit and hospital length of stay, and 6-month mortality.**

Design: **Multicenter, prospective, double-blind, randomized trial.**

Setting: **Twelve intensive care units at Spanish hospitals.**

Patients: **One hundred twenty-seven patients with Acute Physiology and Chronic Health Evaluation II score >12 and requiring parenteral nutrition for 5–9 days.**

Intervention: **Patients were randomized to receive an isonitrogenous and isocaloric total parenteral nutrition or alanine-glutamine dipeptide-supplemented total parenteral nutrition. Nutritional needs were calculated: 0.25 g N/kg^{-1}/d^{-1} and 25 kcal/kg^{-1}/d^{-1}. The study group received 0.5 g/kg^{-1}/d^{-1} of glutamine dipeptide and the control total parenteral nutrition group a similar amount of amino acids. Hyperglycemia was controlled applying an intensive insulin protocol with a target glycemia of 140 mg/dL.**

Measurements and Main Results: **The two groups did not differ at inclusion for the type and severity of injury or the presence of sepsis or septic shock. Caloric intake was similar in both groups. Preprotocol analysis showed that treated patients with alanine-glutamine dipeptide-supplemented total parenteral nutrition had lesser nosocomial pneumonia, 8.04 vs. 29.25 episodes-‰ days of mechanical ventilation ($p = .02$), and urinary tract infections, 2.5 vs. 16.7 episodes-‰ days of urinary catheter ($p = .04$). Intensive care unit, hospital, and 6-month survival were not different. Mean plasmatic glycemia was 149 ± 46 mg/dL in the alanine-glutamine dipeptide-supplemented total parenteral nutrition group and 155 ± 51 mg/dL in the control total parenteral nutrition group ($p < .04$), and mean hourly insulin dose was 4.3 ± 3.3 IU in the alanine-glutamine dipeptide-supplemented total parenteral nutrition group and 4.7 ± 3.7 IU in control total parenteral nutrition group ($p < .001$). Multivariate analysis showed a 54% reduction of the amount of insulin for the same levels of glycemia in the alanine-glutamine dipeptide-supplemented total parenteral nutrition group.**

Conclusions: **Total parenteral nutrition supplemented with alanine-glutamine in intensive care unit patients is associated with a reduced rate of infectious complications and better glycemic control. (Crit Care Med 2011; 39:1263–1268)**

KEY WORDS: L-alanyl-L-glutamine dipeptide; nutrition; insulin sensitivity; critically ill patients

Glutamine represents approximately 60% of muscle-free intracellular amino acids (1, 2) and plays an important role as a nitrogen carrier for urea synthesis and renal ammoniagenesis (3). In conditions of excessive organ or tissue demand of glutamine during episodes of sepsis, after trauma, major surgery, and other catabolic stress situations, endogenous glutamine production may not be sufficient to meet the increased requirement (4). It has been shown that glutamine deficiency is detrimental to several tissues and worsens critically ill patients' outcomes (5). Instability and low solubility hamper addition of native glutamine into parenteral amino acid solutions, but this problem can be overcome by the use of recently developed synthetic glutamine dipeptides (6).

Several studies have shown that alanine-glutamine (Aln-Gln) dipeptide added to parenteral formulas improves nitrogen balance; increases protein synthesis; ameliorates immune function; preserves intestinal barrier permeability; and can reduce morbidity, length of stay, and mortality in critically ill patients (7–9). These beneficial effects can be explained by the fact that glutamine restores intracellular levels of glutathione and modifies the heat shock proteins in critically ill patients (10–12). Furthermore, glutamine can modify fatty acid oxidation and attenuates hyperglycemia and insulin resistance (13). Four days of glutamine supplementation at 0.3 g/kg^{-1}/d^{-1} is necessary to observe significant

***See also p. 1546.**

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changes in plasma glutamine concentration, muscle protein synthesis, and nitrogen balance in patients on total parenteral nutrition (TPN). Most significant clinical results have been obtained with a dose of 0.5 $g/kg^{-1}/d^{-1}$ during 5–10 days (14).

The aim of this study is to assess the clinical benefits of supplemental L-alanyl-L-glutamine TPN treatment in a mixed population of critically ill patients. The primary end point of the study was a complicated clinical outcome, defined by the occurrence of nosocomial infections. Secondary parameters included Sequential Organ Failure Assessment (SOFA) score; hyperglycemia or insulin resistance; and intensive care unit, hospital, and 6-month mortality.

METHODS AND PATIENTS

The study was designed as a controlled, randomized, double-blind, multicenter trial in 12 Spanish ICUs. It was approved by the ethics committee of each hospital according to the Spanish laws. All patients or their closest relative gave written informed consent. The protocol and definitions were previously established in a meeting with the participants using a previous study of our group (15). Fresenius Kabi Spain (Barcelona, Spain) gave financial support to the logistics of the study and supplied the components of both TPN regimes. Our funding sources had no role in the acquisition, analysis, or interpretation of data or in the submission of this report. The protocol was registered in the European trial database with the number EudraCT 2004-001805-90.

Patients. Eligible patients satisfied all of the following criteria: Adult patients, at least 18 yrs old, admitted to the ICU with Acute Physiology and Chronic Health Evaluation II score >12, and requiring parenteral nutrition with either the presence of a contraindication to enteral nutrition or a proven intolerance of enteral feeding over 48 hrs and requiring 5- to 9-day TPN. Patients on mechanical ventilation were sedated with midazolam at 0.3–0.5 mg/kg/hr intravenously and received 2 mg/hr intravenous of morphine for analgesia. Muscle relaxants were used when needed. Exclusion criteria were malnutrition or obesity (body mass index <18.5 or >40 kg/m^2), unstable hemodynamic status (persistent shock, uncontrolled hemorrhage), chronic renal failure requiring dialysis, acute renal failure not treated with hemofiltration or hemodialysis (plasmatic creatinine ≥2.5 mg/dL), hepatic failure with hepatic encephalopathy or portal hypertension, other pre-existing endocrine disorders (amino acid metabolism disease), hyperlipidemia (plasmatic triglyceride levels threefold normal values), continuous infusion of propofol for >24 hrs, chronic maintenance systemic steroid therapy (>0.3 $mg/kg^{-1}/d^{-1}$), immunocompromised patients, pregnant or nursing women, a psychiatric condition making the patient or their relatives unable to understand the nature and scope of the study, and patients with life expectancy <2 days after admission. The following criteria may lead to the exclusion of a patient even after inclusion in the study: necessity to perform major nonscheduled procedures within the study with subsequent TPN discontinuation during more 24 hrs, necessity to administer maximal hourly dose according to insulin protocol, intolerable or serious adverse event, any intercurrent disease likely to interfere with the study, violation of the study protocol, or withdrawal of patient's consent.

Energy Requirements and Diet Administration. Both groups of patients received the TPN infusion as a constant infusion through a central venous catheter. Patients received only glucose and electrolytes solutions in the previous 24 hrs before the study solutions were administered. Patients received the first administration in the first 3 days of ICU admission. Infusion was started at full dose. Nonprotein energy requirements were calculated using the usual body weight and set at 25 $kcal/kg^{-1}/d^{-1}$. Protein requirements were set at 0.25 g $N/kg^{-1}/d^{-1}$. Patients in the Ala-Gln TPN group received 0.5 $g/kg^{-1}/d^{-1}$ of Ala-Gln dipeptide (Dipeptiven, Fresenius Kabi Spain, SA) plus 1.0 $g/kg^{-1}/d^{-1}$ of a standard admixture of amino acids (Vamin 18; Fresenius Kabi Spain, SA). The control group received 1.6 $g/kg^{-1}/d^{-1}$ of the same standard amino acids admixture. Both groups received structured median chain triglyceride/long chain triglyceride lipids. The calorie/nitrogen ratio and glucose–lipid ratio were, respectively, set at 100 and 64/36. Vitamins, trace elements, and electrolytes were administered according to the usual practice of each hospital. The Spanish Pharmacy Registry limits the use of Ala-Gln dipeptide to a maximum of 9 days. If patients needed to be treated after with TPN, Ala-Gln dipeptide was discontinued, and they received the admixture of amino acids used in the control group.

Insulin Administration. Insulin administration was started if the blood glucose level exceed 140 mg/dL. Adjustments of the insulin dose were based on measurements of the whole blood glucose in undiluted arterial blood at 1- to 4-hr intervals with a glucose analyzer. The following protocol for tight glycemic control was used: if the blood glucose exceeds 200 mg/dL despite an insulin administration of a maximum of 10 IU during 3 consecutive hrs, the TPN infusion was decreased by 50%. If the blood glucose exceeds 200 mg/dL, despite the 50% decrease of less than TPN infusion with an insulin administration >10 IU during 3 consecutive hrs, the TPN infusion was stopped. When the blood glucose is between 120 and 200 mg/dL, the TPN infusion was started again. If after restarting, despite a maximal insulin administration, the blood glucose exceeds 200 mg/dL during >3 hrs, the TPN was definitively stopped. Hourly glycemia and the hourly insulin dose were recorded at least 15 times a day.

Outcome Assessment. The primary outcome was the incidence of nosocomial infections acquired throughout the stay in ICU in patients who received at least 4 days of treatment. Nosocomial pneumonia was defined as follows: new onset of purulent sputum; change in character of sputum, respiratory secretions, or suctioning requirements; or worsening gas exchange (e.g., Pao_2/Fio_2 <240, increasing O_2 requirements, or increased ventilation demand) plus two or more serial chest radiographs with new or progressive and persistent infiltrates; consolidation or cavitation; and at least one of the following laboratory findings: positive growth in blood culture not related to another source of infection, positive growth in culture of pleural fluid, positive quantitative culture from minimally contaminated lower respiratory tract specimen (eg, bronchoalveolar lavage or protected specimen brushing) or ≥5% bronchoalveolar lavage-obtained cells contain intracellular bacteria on direct microscopic exam (eg, Gram-negative stain). Other nosocomial infections were defined according the last Centers for Disease Control and Prevention guidelines (16). Two investigators blinded to the treatment allocation validated the diagnosis of infection, and each infection at each site was considered as a separate infectious complication. Secondary outcomes were the changes in the daily SOFA score using Δ-SOFA score. Other secondary end points were: days of stay in the ICU and hospital, overall all-cause mortality during the ICU stay, and 6-month mortality. Hyperglycemia and insulin needs were also analyzed to assess the effect of glutamine on insulin resistance.

Treatment Assignment. Patients were randomized to receive either Ala-Gln TPN or control TPN. Allocation to treatment was done with a computer-generated random numbers table with a minimization program and two stratification levels: site and the Acute Physiology and Chronic Health Evaluation II score. Each center recruited a minimum of six cases and competitive recruitment was allowed until any center reached a maximum of 18 patients. Investigators remained blinded until the end of the study for treatment group, diagnosis of nosocomial infection, statistical analysis, and the final number of patients recruited.

Data Management and Statistical Analysis. The sample size calculation was based on the results of a multicenter clinical trial that showed a significant decrease in clinical outcomes in the glutamine recipients when using a proportion difference of 30%. The number of patients needed was 128 with an α error of 0.5 and a β error of 20%. Investigators fulfilled the forms included in the database through a secure web site designed for this study. At least each center was monitored twice for reviewing the inclusion and exclusion criteria and the adherence to the protocol including allocation

concealment. Continuous data were assessed for normality and two-tailed Student's t test was performed for normal data and the Mann-Whitney U test for nonnormal distributions. Two-tailed chi-square test was applied for proportions. The Δ-SOFA changes were analyzed using a multivariate analysis of the intergroup variance. Relative risk with 95% confidence interval was calculated for the incidence of nosocomial infections. We planned an intent-to-treat analysis and per-protocol analysis in patients who received at least 4 days of treatment. Six-month survival probability was analyzed using the Kaplan-Meier test. After an exploratory analysis, glycemia and insulin values were brushed. To compare both groups, six different time series models were applied to find the model that better fits using the root mean-square error between patients and individual determinations. The model that better fits was an autoregressive moving average model (1, 2), in which 1 and 2 mean the plasmatic glycemia, 1 and 2 hrs before the next determination. Because glycemia and insulin data were unbalanced, we applied a hierarchical mixed linear model that overcomes the limitations of multivariate analysis of variance. We used two levels of hierarchy, patient and measurement, to identify the effect of insulin dose and the type of diet (17). A lineal and sinusoidal model was used to assess the glycemia circadian rhythm.

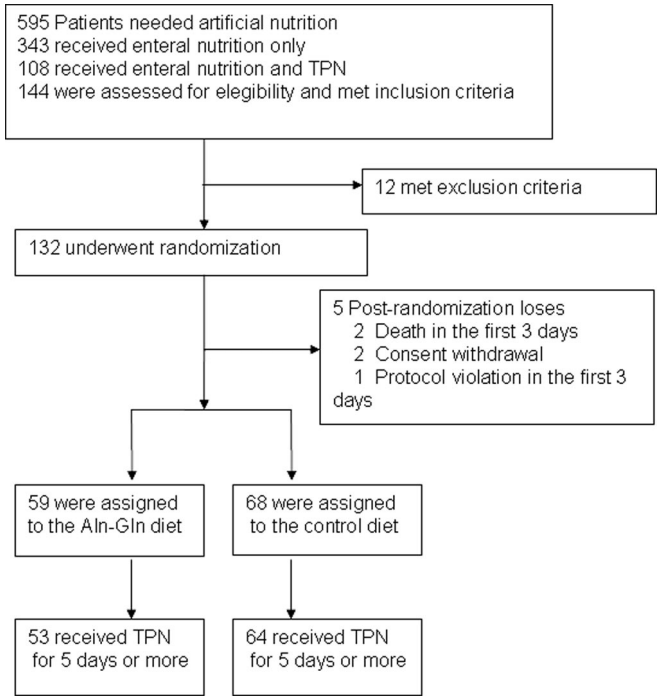

Figure 1. CONSORT statement. *Ala-Glu*, alanine-glutamine; *TPN*, total parenteral nutrition.

RESULTS

One hundred thirty-two patients were randomized and five patients were lost. One hundred twenty-seven patients received any treatment and 117 completed 4 days of nutritional support (Fig. 1). Demographic data were similar in the intent-to-treat and per-protocol analysis. The Ala-Gln group had a higher incidence of cancer on admission, 25 (42%) vs. 16 (24%) ($p < .01$). There were no differences in the number of patients infected on admission, the incidence of severe sepsis, or septic shock on admission (Table 1). Both groups had similar caloric requirements and received the same amount of calories and protein across the study period (Table 2). No significant adverse events that warranted TPN withdrawal were recorded.

Primary Outcome. The incidence of nosocomial infections was significantly lower among patients receiving Ala-Gln TPN than among control patients (Table 3). In the intent-to-treat analysis, the Ala-Gln TPN group had lesser urinary tract infections than control patients, 2.3% vs. 16.9% urinary catheter days (relative risk, 0.6; 95% confidence interval, 0.5–0.8; $p = .03$). Other nosocomial infections, the number of infections per patient, and the number of infected patients were similar in both groups. In the per-protocol analysis, Aln-Gln TPN group had lesser nosocomial pneumonias than the control group, eight vs. 29 episodes-% days of mechanical ventilation (relative risk, 0.7; 95% confidence interval, 0.6–0.9; $p = .02$) and urinary tract infections, 2.4% vs. 17% urinary catheter days (relative risk, 0.6; 95% confidence interval, 0.5–0.8; $p = .04$). Isolated specimens causing pneumonia are shown in Table 4.

Glycemic Control. The best model of fitness was an autoregressive moving average model (1, 2) with a root mean-square error of 24.5. The effect of insulin dose on plasmatic glycemia was best measured using a regression model with autocorrelation with one previous measurement ($\beta = -0.94$; $p < .0001$). When looking to the effect of the different diets, the Aln-Gln TPN group needed lesser insulin than the control group (β control group − β Ala-Gln TPN group $= -0.54$; $p < .0001$), which means a 54% reduction of the amount of insulin for the same levels of plasmatic glycemia (Table 4). We were unable to find circadian differences between the doses of insulin in both groups.

Secondary End Points. SOFA score Δ-SOFA for each day were similar in both groups. ICU length of stay or hospital stay was similar in both groups and ICU and hospital mortality did not achieve significant differences. Six-month mortality was similar in both groups but lower than predicted by the Acute Physiology and Chronic Health Evaluation II scores.

DISCUSSION

This randomized, double-blind, multicenter study shows that adult critically ill patients treated at least for 4 days with an Aln-Gln-supplemented TPN had lesser nosocomial pneumonias and urinary tract infections and had better tight glycemic control. Both groups of patients were similar in terms of age, type of disease, and severity scores. Caloric intake was similar in both groups and TPN was well tolerated in both groups. The efforts made to conceal the patients ' treatment assignments using a minimization program and competitive recruitment resulted in two groups of mismatched size and the Aln-Gln TPN group had a higher incidence of cancer on admission. Concerns about selection bias are minimized by the fact that both groups had similar baseline characteristics. Furthermore, the higher incidence of cancer in the study group can reinforce the effect of Aln-Gln-enriched TPN. Another caveat of our study is the duration of treatment. The Spanish Drug Agency limits the use of Aln-Gln dipeptides to 9 days and it is uncertain if all patients had achieved normal plasmatic glutamine levels.

Table 1. Demographic data

	Ala-Gln TPN	Control TPN	*p*
Intent-to-treat analysis			
Number of patients	59	68	
Sex, female	22 (37%)	23 (34%)	.7
Age	68 (51–76)	65 (50–72)	.3
APACHE II	19 (15–21)	18 (15–23)	.8
SOFA	6 (4–9)	7 (4–9)	.7
GCS	15 (13–15)	15 (13–15)	.4
Primary diagnosis			
Trauma	14	17	
Hemorrhagic shock	1	2	
Surgery for GI cancer[a]	25	16	.5
Postoperative respiratory failure	1	2	
GI perforation/obstruction	12	23	
Other GI tract diseases	6	8	
Hemodialysis/hemofiltration	14 (24%)	17 (25%)	8
Mechanical ventilation	44 (75%)	53 (78%)	.6
Days of mechanical ventilation	4 (1–9)	5 (1–8)	.8
Infected patient	34 (58%)	38 (56%)	.8
Sepsis on admission	31 (53%)	34 (50%)	.8
Septic shock on admission	16 (27%)	14 (21%)	.4
ICU LOS	12 (7–22)	12 (7–24)	.7
Hospital LOS	35 (23–56)	31 (20–58)	.6
ICU mortality	9 (16%)	13 (20%)	.6
6-month mortality	16 (28%)	23 (34%)	.5
Treated patients			
Number of patients	53	64	
Sex, female	19 (36%)	23 (36%)	.9
Age	68 (48–72)	65 (50–72)	.5
APACHE II	19 (14–23)	17 (14–22)	.5
Predicted mortality	35% (19–48)	33% (17–42)	.4
SOFA	6 (3–8)	7 (4–10)	.5
GCS	15 (13–15)	15 (13–15)	.8
Primary diagnosis			
Trauma	12	14	
Hemorrhagic shock	1	2	
Surgery for GI cancer[b]	23	14	
Postoperative respiratory failure	1	2	
GI perforation/obstruction	12	23	
Other GI tract diseases	4	8	
Hemodialysis/hemofiltration	10 (19%)	16 (25%)	.4
Mechanical ventilation	38 (72%)	50 (78%)	.3
Days of mechanical ventilation	4 (1–9)	5 (1–9)	.5
Infected patient	30 (57%)	35 (55%)	.8
Sepsis on admission	28 (53%)	31 (48%)	.6
Septic shock on admission	14 (27%)	12 (19%)	.3
ICU LOS	12 (7–23)	12 (7–24)	.5
Hospital LOS	36 (24–56)	33 (22–59)	.6
ICU mortality	8 (15%)	11 (18%)	.7
6-month mortality	13 (25%)	21 (33%)	.4

Ala-Gln, alanine-glutamine; TPN, total parenteral nutrition; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; GCS, Glasgow Coma Score; GI, gastrointestinal; ICU, intensive care unit; LOS, length of stay.

[a]$p = .02$; [b]$p = .001$.

Glutamine is actually recommended for trauma and burned critically ill patients (18). Many clinical studies had shown that parenteral glutamine could improve the outcome in critically ill patients (14, 19–22). Two additional meta-analyses had shown that glutamine decreases the incidence of nosocomial infections and can decrease overall mortality (23, 24). These results are conflicting and there is a debate between different authors (25, 26). The two meta-analyses included studies in which different amounts of glutamine were administered enterally or parenterally and the studied populations were heterogeneous. The two meta-analysis that looked at the glutamine dose have shown that a dose of glutamine higher than 20 g/day is needed to achieve any significant effect (21, 27). Indeed, some authors have suggested that doses of 20–25 g/day are no needed to normalize plasma concentration (28). Experimental studies have shown that intravenous glutamine avoids glutamine tissue depletion and improves protein metabolism (29, 30) and restores glutathione levels and serum heat shock protein 70 in critically ill patients (31, 32). Putting this together, intravenous glutamine supplementation can improve protein metabolism and increases the immune response in critically ill patients. Previous studies using a dose of 0.5 g/kg/day of parenteral glutamine dipeptide have shown a decreased incidence of nosocomial infections in surgical, pancreatitis, and trauma patients (31, 33, 34). There is at least one ongoing large trial that will examine the effect of different doses of glutamine on mortality as the primary end point (32).

These data support the use of 0.5 g/kg/day of Aln-Gln dipeptide and corroborates our hypothesis that high doses of glutamine have beneficial effects in terms of new infectious complications in an heterogeneous population of critically ill patients and confirms the findings described by other authors (33). We have presented our data using the incidence ratio of infections, as proposed by the Centers for Disease Control and Prevention, to overcome the effect of the length of stay over the infection rate. Nevertheless, our results are quite similar to other previously published work but with stronger significance if we use the absolute values (35).

Our data showed that Aln-Gln dipeptide decreases the needs of insulin and allows better control of plasmatic glycemia when using tight glycemic control. Furthermore, as the time series analysis shows, this effect is independent irrespective of the insulin dose administered. Experimental studies suggest that glutamine modifies fatty acid oxidation, increases glucose use, and increases insulin sensitivity (36, 37). Our results confirm the results of two previous clinical studies that addressed a similar question but without using tight glycemic control (33, 38). Recently, a study has demonstrated that trauma critically ill patients had insulin resistance measured with the euglycemic hyperinsulinemic clamp that could be reversed with intravenous Aln-Gln dipeptide (39).

CONCLUSIONS

Critically ill patients treated with Ala-Gln dipeptide-supplemented TPN, in a dosage of 0.5 g (corresponding to 0.33 g of Gln) per kilogram of body weight per day,

Table 2. Caloric requirements and administration across the study[a]

	Ala-Gln TPN	Control TPN	Total	p
No. of patients	59	68	127	
Actual BW	73 (65–82)	70 (64–80)	70 (65–80)	.4
Usual BW	75 (65–83)	75 (65–80)		.4
Height	167 (156–175)	167 (161–175)	166 (160–175)	.9
BMI	25.4 (23.9–27.3)	25.4 (23.5–27.7)	25 (23.7–27.6)	.8
Days on TPN	6 (5–8)	5 (4–8)	6 (4–8)	.7
Patients fed with TPN ≥5 days	53 (90%)	64 (94%)	117 (92%)	.4
Patients switched to EN	3 (5%)	5 (7%)	8 (6%)	.7
Caloric requirements	1716 ± 500	1703 ± 477	1709 ± 486	.9
Caloric intake day 1	1827 ± 276	1806 ± 291	1816 ± 283	.7
Caloric intake day 2	1827 ± 275	1805 ± 297	1815 ± 286	.7
Caloric intake day 3	1823 ± 281	1797 ± 295	1809 ± 287	.6
Caloric intake day 4	1823 ± 279	1796 ± 296	1809 ± 287	.6
Caloric intake day 5	1820 ± 283	1786 ± 288	1802 ± 285	.5
Caloric intake day 6	1825 ± 295	1863 ± 301	1845 ± 297	.6
Caloric intake day 7	1852 ± 275	1875 ± 309	1864 ± 290	.4
Caloric intake day 8	1843 ± 299	1870 ± 340	1857 ± 318	.1
Caloric intake day 9	1835 ± 305	1837 ± 331	1836 ± 315	.4
Nitrogen intake, g/day, day 1	18.3 ± 2.8	18.1 ± 2.9	18.2 ± 2.9	.2
Nitrogen intake, g/day, day 2	18.3 ± 2.7	18.1 ± 3	18.2 ± 2.9	.2
Nitrogen intake, g/day, day 3	18.2 ± 2.8	18 ± 2.9	18.1 ± 2.9	.3
Nitrogen intake, g/day, day 4	18.2 ± 2.8	18 ± 3	18.1 ± 2.9	.2
Nitrogen intake, g/day, day 5	18.2 ± 2.8	17.9 ± 2.9	18 ± 2.8	.4
Nitrogen intake, g/day, day 6	18.3 ± 3	18.3 ± 2.13	18.3 ± 2.13	.4
Nitrogen intake, g/day, day 7	18.3 ± 2.14	18.6 ± 3	18.3 ± 2.14	.1
Nitrogen intake, g/day, day 8	18.3 ± 2.15	18.3 ± 2.15	18.5 ± 3	.08
Nitrogen intake, g/day, day 9	18.4 ± 3	18.7 ± 3.4	18.6 ± 3.2	.08
Mean glycemia, mg/dL	149 ± 46	155 ± 51	152 ± 50	.04
Mean insulin, UI/hr	4.3 ± 3.3	4.7 ± 3.7	4.5 ± 3.3	.001

Ala-Gln, alanine-glutamine; TPN, total parenteral nutrition; BW, body weight; BMI, body mass index; EN, enteral nutrition.

[a]Data are expressed as median and interquartile range, except for glycemia and insulin expressed as mean ± SD.

Table 3. Infectious outcomes

	Ala-Gln TPN	Control TPN	Total	RR (95% CI)	p
Intent-to-treat analysis					
No. of patients	59	68	127		
Infected patients (%)	24 (41%)	31 (46%)	55 (43%)	0.9 (0.6–1.3)	.6
Nosocomial pneumonia (no. 1.000 ventilator days)	13.5	27.2	21.1	0.4 (0.2–1.3)	.1
Primary bacteremia (no. 100 ICU days)	0.6	0.8	0.7	0.7 (0.3–2.1)	.6
Catheter-related sepsis (no. 100 catheter days)	1.8	1.1	1.4	1.6 (0.4–7.5)	.5
UTI (no. 1000 catheter days)	2.3	16.3	9.7	0.6 (0.45–0.8)	.03
Surgical infection (%)	13 (22%)	17 (25%)	30 (23%)	0.8 (0.5–1.7)	.7
Number of infections/patient	1.5	2.4	—	—	.3
Treated patients					
No. of patients	53	64	117		
Infected patients (%)	22 (42%)	31 (48%)	53 (45%)	0.8 (0.4–1.6)	.5
Nosocomial pneumonia (no. 1.000 ventilator days)	8.0	29.3	20.7	1.4 (1.2–1.7)	.02
Primary bacteremia (no. 1000 ICU days)	5.8	8.7	7.4	1.2 (0.8–1.7)	.5
Catheter-related sepsis (no. 1000 catheter days)	14.5	5.1	1.4	0.3 (0.1–1.7)	.1
UTI (no. 1000 catheter days)	2.5	16.7	10.2	1.6 (1.3–2.1)	.04
Surgical infection (%)	12 (23%)	17 (27%)	29 (25%)	0.4 (0.3–1.9)	.6
Number of infections/patient	1.5	2.1	—	—	.2

Ala-Gln, alanine-glutamine; TPN, total parenteral nutrition; RR, relative risk; CI, confidence interval; ICU, intensive care unit; UTI, urinary tract infection.

Table 4. ARMA (1, 2) time-series analysis and mixed hierarchical linear model of glycemia insulin needs and the effect of the types of diet

	β	SE (β)	p
ARMA (1, 2)[a]			
Insulin dose	7.14	0.24	<.001
Insulin 1 hr before	−0.94	0.13	<.0001
Linear model[b]			
Control TPN	−0.8	0.1	<.0001
Ala-Gln TPN	−1.1	0.2	<.0001
Difference	−0.5	0.1	<.0001

TPN, total parenteral nutrition; Ala-Gln, alanine-glutamine.

[a]Autoregressive moving average model in which 1 and 2 mean the plasmatic glycemia 1 and 2 hrs before the next determination; [b]hierarchical mixed linear model.

can decrease the incidence of nosocomial infections, particularly nosocomial pneumonia and urinary tract infection, prevents worsening of hyperglycemia, and decrease the need for exogenous insulin in critically ill patients. There is enough evidence to support the use of intravenous glutamine given at dose of 0.5 g/kg/day because it improves clinical outcomes of critically ill patients. Further studies should be done to identify the adequate dose that maximizes these beneficial effects, and larger studies are needed to look at the incidence of organ failure and mortality.

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