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ORIGINAL

A randomized trial of intravenous glutamine supplementation in trauma ICU patients

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Take-home message: Intravenous glutamine dipeptide supplementation did not result in a decrease of new infections in trauma ICU patients. Low plasma glutamine levels at day 6 were associated with a worse outcome.

Electronic supplementary material
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Abstract *Purpose:* To evaluate the effect of the intravenous (i.v.) L-alanyl-L-glutamine dipeptide supplementation during 5 days on clinical outcome in trauma patients admitted to the intensive care unit (ICU). *Methods:* This was a prospective, randomized, double-blind, multicenter trial. Glutamine was not given as a component of nutrition but as an extra infusion. The primary outcome variable was the number of new infections within the first 14 days. *Results:* We included 142 patients. There were no differences between groups in baseline characteristics. Up to 62 % of the patients in the placebo group and 63 % in the treatment group presented confirmed infections ($p = 0.86$). ICU length of stay was 14 days in both groups ($p = 0.54$). Hospital length of stay was 27 days in the placebo group and 29 in the treatment group ($p = 0.88$). ICU mortality was 4.2 % in both groups ($p = 1$). Sixty percent of the patients presented low glutamine levels before randomization. At the end of the treatment (6th day), 48 % of the patients maintained low glutamine levels (39 % of treated patients vs. 57 % in the placebo group). Patients with low glutamine levels at day 6 had more number of infections (58.8 vs. 80.9 %; $p = 0.032$) and longer ICU (9 vs. 20 days; $p < 0.01$) and hospital length of stay (24 vs. 41 days; $p = 0.01$). *Conclusions:* There was no benefit with i.v. L-alanyl-L-glutamine dipeptide supplementation (0.5 g/kg body weight/day of the dipeptide) during 5 days in trauma patients admitted to the ICU. The i.v. glutamine supplementation was not enough to normalize the plasma glutamine levels in all patients. Low plasma glutamine levels at day 6 were associated with a worse outcome.

Keywords Trauma · Intravenous glutamine supplementation · Pharmaconutrition · Infections · Outcome

Introduction

Multiple trauma is a life-threatening condition, not only from the trauma itself but also from the subsequent immunological dysfunctions and metabolic alterations that appear after the trauma [1]. This impairment in the immune response is associated with an increased rate of infectious complications and death [2, 3]. Infectious complications in critically ill patients are independently associated with higher mortality rates [4].

Glutamine, traditionally considered as a non-essential amino acid under physiological conditions, has received considerable attention during catabolic states such as trauma. Under these conditions, there is a severe depletion of glutamine levels in plasma [5–8]. It has been reported that a low plasma glutamine level at intensive care unit (ICU) admission is an independent risk factor for mortality [9].

Numerous trials have documented beneficial effects of glutamine supplementation in critically ill patients [6, 10–14]. In patients receiving parenteral nutrition (PN), glutamine supplementation was associated with improved clinical outcomes in terms of improved survival rate, decreased infections, costs, and reduced hospital length of stay [10–13, 15]. However, recently published trials failed to demonstrate any beneficial effect of supplementation of total PN [16–18].

Nevertheless, PN is not the initial route of feeding in the majority of patients admitted to the ICU. The enteral feeding route is preferred for critically ill patients because of its reduced costs and risk of infective complications [19, 20]. Glutamine supplementation in patients receiving enteral nutrition and its best route are still debated [21–25].

To overcome the problem of not reaching the target dose by the enteral route, and the possibility of altered gut absorption capacity, different trials investigated the effect of intravenous glutamine supplementation in patients receiving enteral nutrition [26–30]. However, these trials were pilot studies and evaluated surrogate outcomes. As a consequence, at the moment there are insufficient data to generate recommendations for intravenous glutamine supplementation in critically ill patients receiving enteral nutrition.

Thus, we have designed this trial on the basis of the concept of pharmaconutrition. This treatment paradigm embraces the fact that nutrients (such as glutamine) have profound effects on underlying inflammatory, immunological, metabolic, and other pathophysiological processes, so that they can modulate the underlying illness and therefore influence outcome.

Therefore, in this multicenter study, we evaluated the effect of the dipeptide L-alanyl-L-glutamine as a pharmaconutrition treatment on clinical outcome in 142 trauma patients admitted to the ICU.

Methods

The study was approved by the ethics committee of each hospital according to Spanish law and therefore has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients or their closest relative gave written informed consent.

This was a controlled, randomized, double-blind, multicenter trial.

This trial was supported by a grant from the Ministerio de Sanidad y Consumo of Spain. Fresenius-Kabi Spain gave support by facilitating with the empty bottles for the placebo to appropriately implement blinding. Our funding source had no role in the acquisition, analysis, or interpretation of the data or in the submission of this report. The protocol was registered at ClinicalTrials.gov as NCT01250782.

Patients

Eligible patients satisfied all of the following criteria: adult patients aged at least 18 years old and less than 75 years old, admitted to the ICU with a diagnosis of multiple trauma with an injury severity score of at least 10 points, requiring enteral nutrition and/or PN, and expected length of stay in the ICU at least 48 h.

Informed consent was mandatory in all cases. The exclusion criteria were: age less than 18 years or older than 75 years, significant hepatic failure (patients with Child C cirrhosis), severe renal failure (glomerular filtration less than 25 mL/min), pregnancy, patients not expected to be in the ICU for more than 48 h (owing to imminent death), weight greater than 110 kg, or enrolled in another study.

Patient management

All patients were managed according to protocols established for trauma patients based on the recommendations of Advanced Trauma Life Support [31] and adapted by the Spanish National Society of Intensive Care Medicine [32].

Nutrition support was based on current guidance from the European Society for Clinical Nutrition and Metabolism (ESPEN) [33]. At ICU admission the nutritional target for all admitted patients was a caloric intake of 28 kcal/kg/day. Protein administration, without glutamine, was set at 1–2 g/kg/day. The choice between enteral or PN or a combination was left to the attending physician's discretion. Enteral nutrition was targeted to be initiated within 24 h of ICU admission, and the aim was to reach the target goal by day 3. If enteral nutrition was

contraindicated or failed to reach the target goal by day 3, PN was started.

Enteral nutrition was administered continuously by the primary care team according to routine protocols as semirecumbent positioning, preferred use of nasogastric tubes, and the use of prokinetic agents if necessary (metoclopramide and/or erythromycin). Enteral nutrition (which consisted of polymeric formulas) and total PN contained 1–1.25 kcal/mL of energy (approximately 20 % of proteins, 30 % of lipids, and 50 % of carbohydrates).

Continuous intravenous administration of insulin was used to maintain blood glucose at lower than 150 mg/dL according to clinical protocols, and arterial blood glucose was checked at least four times a day. Hyperglycemia was defined as a blood glucose concentration higher than 150 mg/dL and hypoglycemia as lower that 60 mg/dL. Trace elements, minerals, and vitamins were administered daily as recommended by European guidelines [33].

Patients on mechanical ventilation were sedated with midazolam 0.3–0.5 mg/kg/h intravenously or propofol 2 mg/kg/h and received morphine or remifentanil intravenously for analgesia. Muscle relaxants were used as needed.

Treatment assignment

The study treatments (L-alanyl-L-glutamine dipeptide or placebo) were randomly assigned to the patient at the study sites by means of a computer program. In each hospital there were a limited number of treatments sent from the Son Espases University Hospital pharmacy that were numerated and used in strict chronological ascending order. Both sets of bottles (Ala-Gln and placebo) were labeled identically in the pharmacy and the two solutions were indistinguishable. All patients, investigators, and coworkers were unaware of treatment allocation and remained blinded until the final statistical evaluation was completed.

Composition of regimens

The study nutrient (Dipeptide, Fresenius-Kabi, Bad Homburg, Germany) was procured thanks to a public grant from the Spanish government. This group received Ala-Gln (0.5 g/kg body weight/day of the dipeptide; 0.35 g of L-glutamine/kg body weight/day) by continuous intravenous infusion (24 h/day) through a dedicated lumen via central venous access during 5 days. Two bottles of Dipeptide were added to 1,000 mL of normal saline and then infused into the patient and adjusted for patient weight. This perfusion was changed every 24 h during the 5 days of treatment. The dose and the duration of the treatment were in keeping with contemporary guidelines on nutritional support when the study was designed.

The control group received placebo (normal saline; 0.9 % NaCl) by continuous intravenous infusion, adjusted for patient weight and during 5 days. The preparation of the infusion bag in the control group was identical to the treatment group.

As a result of this strategy both groups did not receive isonitrogenous and isocaloric nutrition. The use of normal saline as placebo is justified by the fact that there is no evidence that a difference in some grams of nitrogen is related to the patients' survival. Moreover, evidence suggests that the benefit of the glutamine is not related to the nitrogen but to its effects on the inflammatory and immunological events. On the other hand, some of the amino acids used as placebo to make an isonitrogenous and isocaloric regimen could also have some effects.

Primary variables

The primary outcome variable was the proportion of participants with new infections within the first 14 days after randomization. All infection reports were validated separately by two investigators blinded to the treatment allocation (I.A., A.O.). Infectious episode was confirmed in accordance with the Centers for Disease Control (CDC) criteria [34]. See Supplementary Material 1 for a complete description of the definitions used.

Other outcome measures defined were ICU and hospital length of hospital, ICU and hospital mortality rate, and sequential organ failure assessment (SOFA) score [35] evaluated before and after the treatment period.

Other objectives of the study included a priori were to evaluate the efficacy of the Ala-Gln dipeptide in different patients regarding their severity, specifically in patients with an ISS of at least 25 and patients with low plasma levels of glutamine.

Glutamine levels

Glutamine levels in plasma were measured by high-performance liquid chromatography (HPLC) before treatment was started and at the end of the treatment (day 6). Normal ranges of glutamine measured by HPLC are 335–635 μmol/L.

Statistical analysis and sample size

Statistical analysis was performed using IBM SPSS Statistics 20.0. A baseline comparison of demographics, severity of illness, and baseline measures was carried out between each group, using a combination of *t* test and Chi-squared tests. Normally distributed continuous data

were analyzed by a parametric test (Student t test or ANOVA) and reported as mean ± SD. Non-normally distributed continuous data were analyzed with a non-parametric test (Mann–Whitney U test) and reported as median ± Q1–Q3. Data were analyzed on the basis of intention to treat analysis.

The primary endpoint of the trial was the number of infectious complications in the group of traumatic patients admitted to the ICU. Previous studies [13] indicate that the expected reduction in infections would be 18 % (from 58 to 40 %). On the basis of the data available from national infection surveillance in Spain [36, 37], 20.6 % of trauma patients admitted to the ICU got a complication with at least one infectious episode. Hence, 722 participants would be required to detect this size of difference (with 80 % power and $2p < 0.05$).

We planned to include 150 patients to better define the group of patients that can be enrolled in such a trial and to confirm the sample size required.

Results

The trial was conducted in four centers in Spain and was opened for enrollment from October 2010 to October 2012. In total 198 patients were screened for eligibility, of which 56 were excluded and 142 were included (see Fig. 1 in the Electronic Supplementary Material).

Baseline characteristics

Baseline characteristics were well matched across groups (Table 1).

Albumin, pre-albumin, weight, and the time to start the infusion of the glutamine/placebo were equal in both groups. The percentages of patients who required enteral nutrition, total PN, or both were also similar.

Primary outcomes: new infections, length of stay, and mortality

Primary outcome measures are shown in Table 2. Using the definition of confirmed infections proposed by the CDC, there was no evidence of any beneficial effect from the Ala-Gln dipeptide. The overall number of infected patients in the first 14 days after hospital admission was 89 (62.6 %).

ICU mortality was 4.2 % in both groups and in-hospital mortality was 5.9 %. Again, there was no evidence of any beneficial effect from the dipeptide in terms of mortality.

Table 1 Baseline characteristics of 142 trauma patients included in the study

Characteristic	Placebo ($N = 71$)	L-Alanyl-L-glutamine ($N = 71$)	p value
Age (years)	39 (28–52)	43 (30–59)	0.191
Female (%)	9 (12.7)	12 (16.9)	0.478
Previous disease[a]	30 (49.2)	28 (44.4)	0.597
Thoracic trauma	44 (62.0)	45 (63.4)	0.862
Abdominal trauma	13 (18.3)	14 (19.7)	0.831
Pelvic trauma	39 (54.9)	34 (47.9)	0.401
Spine trauma	9 (12.7)	9 (12.7)	1.0
Severe TBI	29 (40.8)	31 (43.7)	0.734
Moderate TBI	20 (28.2)	20 (28.2)	1.0
Surgery before randomization	29 (40.8)	28 (39.4)	0.864
Hemorrhagic shock before randomization	11 (15.7)	18 (25.7)	0.144
Injury severity score	32 (25–41)	32 (25–43)	0.959
SOFA values prior to randomization	7 (4–8)	6 (4–8)	0.690
Albumin prior to randomization (g/L)	30.2 (24.9–34.0)	28.0 (23.3–33.0)	0.444
Pre-albumin prior to randomization (mg/dL)	16.1 (12.2–21.5)	16.0 (12.4–21.0)	0.859
Weight (kg)	80.0 (71.8–82.3)	78.0 (67.6–84.5)	0.093
Time to initiation infusion (mins)	1,757 (1,234–2,595)	1,680 (1,395–2,468)	0.944
Enteral nutrition	46 (65.7)	41 (58.6)	0.491
Parenteral nutrition	7 (10.0)	7 (10.0)	0.531
Both types of nutrition	18 (24.3)	23 (31.4)	0.351
Basal glutamine levels[b]	306 (242–376)	312 (260–412)	0.539

Values are numbers of patients (percentages) or median and interquartile range

SOFA sequential organ failure assessment score, *Severe TBI* traumatic brain injury Glasgow coma scale <8 points on admission, *Moderate TBI* traumatic brain injury Glasgow coma scale 9–13 points on admission

[a] Positive past medical history prior to the accident

[b] Normal range of plasma glutamine measured by HPLC (335–635 μmol/L)

Table 2 Infections, mortality, and length of stay in the 142 trauma patients included in the study

Characteristic	Placebo ($N = 71$)	L-Alanyl-L-glutamine ($N = 71$)	p value
Number of infected patients	44 (62.0)	45 (63.4)	0.862
Confirmed respiratory tract infection	33 (46.5)	37 (52.1)	0.502
Nosocomial pneumonia	21 (29.6)	23 (32.4)	0.856
Tracheobronchitis	12 (16.9)	14 (19.7)	0.828
Confirmed urinary tract infection	3 (4.2)	4 (5.6)	0.999
Primary bacteremia	11 (15.1)	9 (12.7)	0.809
Other confirmed infections	12 (16.9)	15 (21.1)	0.669
Antibiotic used	54 (87.1)	58 (89.2)	0.710
Days of mechanical ventilation (days)	9.5 (5–18.5)	9.0 (3–18)	0.653
SOFA	5 (3–7)	5 (3–8)	0.922
ICU length of stay (days)	14 (7–24)	14 (8–28)	0.541
Hospital length of stay (days)	27 (16–46)	29 (17–47)	0.887
ICU mortality	3 (4.2)	3 (4.2)	0.999
Hospital mortality	5 (7.1)	4 (5.6)	0.620
Glutamine day 6	322 (274–361)	380 (302–476)	0.005

Values are numbers of patients (percentages) or median and interquartile range. Confirmed infections were in accordance with Centers for Disease Control definition
SOFA sequential organ failure assessment score

Table 3 Prespecified subgroup analyses of infections, mortality, and length of stay among patients with an ISS score greater than 24

Characteristic	Placebo ($N = 42$)	L-Alanyl-L-glutamine ($N = 40$)	p value
Number of infected patients	36 (62.1)	35 (64.8)	0.763
Confirmed respiratory tract infection	21 (50.0)	21 (52.5)	0.860
Nosocomial pneumonia	12 (28.6)	16 (40.0)	0.076
Tracheobronchitis	9 (21.4)	5 (12.5)	0.435
Confirmed urinary tract infection	2 (3.4)	4 (7.4)	0.352
Primary bacteremia	7 (12.0)	7 (13.0)	0.886
Other confirmed infections	10 (17.2)	14 (30.0)	0.374
ICU length of stay (days)	16 (8–25)	16 (10–30)	0.588
Antibiotic used	47 (90.4)	44 (88.0)	0.698
Days of mechanical ventilation	12 (6–21)	10 (3–19)	0.470
SOFA	6 (3–8)	5 (3–7)	0.471
Hospital length of stay (days)	30 (18–55)	31 (17–48)	0.885
ICU mortality	2 (3.4)	3 (5.6)	0.589
Hospital mortality	4 (6.9)	4 (7.5)	0.602
Glutamine baseline[a]	307 (238–380)	311 (243–387)	0.928
Glutamine day 6[a]	311 (267–355)	343 (288–467)	0.012

Values are numbers of patients (percentages) or median and interquartile range. Confirmed infections were in accordance with Centers for Disease Control definition
SOFA sequential organ failure assessment score
[a] Normal range of plasma glutamine measured by HPLC (335–635 μmol/L)

Laboratory substudy

Baseline and day 6 plasma glutamine levels were measured in a subgroup of 100 patients. Of these, 60 % of the patients presented low glutamine levels before randomization (58 % of the patients in the treatment group and 62 % of the patients in the placebo group). At the end of the treatment (day 6), 48 % of the patients maintained low glutamine levels (39 % of the patients in the treatment group and 57 % of the placebo group). Glutamine supplementation as compared with no glutamine was associated with a significant increase in plasma glutamine levels on day 6 ($p = 0.03$).

Interestingly, in those patients with higher ISS it was more difficult to achieve normal glutamine levels (see Fig. 2 in the Electronic Supplementary Material) compared to those with lower ISS.

Further analysis

A priori analysis based on patients who had higher ISS and lower glutamine levels was also performed. Table 3 shows the results of the 82 patients who had an ISS greater than 24 points. Glutamine supplementation as compared with no glutamine did not have a significant

Table 4 Prespecified subgroup analyses of infections, mortality, and length of stay among patients with basal low glutamine levels

Characteristic	Normal basal glutamine levels ($N = 40$)	Low basal glutamine levels ($N = 60$)	p value
Number of infected patients	25 (62.5)	44 (73.3)	0.251
Confirmed respiratory tract infection	25 (62.5)	30 (50.0)	0.305
Nosocomial pneumonia	16 (40.0)	20 (33.3)	0.640
Tracheobronchitis	9 (22.5)	10 (16.7)	0.640
Confirmed urinary tract infection	3 (7.5)	2 (3.3)	0.349
Primary bacteremia	5 (12.5)	9 (15.0)	0.851
Other confirmed infections	8 (20.0)	14 (23.3)	0.458
ICU length of stay (days)	13 (7–25)	13 (7–24)	0.891
Antibiotic used	36 (92.3)	50 (84.7)	0.264
Days of mechanical ventilation	8 (4–19)	8 (5–19)	0.946
SOFA	7 (3–9)	6 (3–7)	0.126
Hospital length of stay (days)	27 (15–48)	30 (17–55)	0.458
ICU mortality	3 (7.5)	2 (3.3)	0.349
Hospital mortality	4 (10.1)	3 (5.0)	0.766
Glutamine baseline[a]	422 (370–536)	263 (228–305)	<0.001
Glutamine day 6[a]	349 (302–445)	325 (271–397)	0.105
ISS	32 (25–509)	26 (25–41)	0.496
Age (years)	41 (27–52)	42 (29–59)	0.314

Values are numbers of patients (percentages) or median and interquartile range. Confirmed infections were in accordance with Centers for Disease Control definition

SOFA sequential organ failure assessment score, *ISS* injury severity score

[a] Normal range of plasma glutamine measured by HPLC (335–635 μmol/L)

Table 5 Prespecified subgroup analyses of infections, mortality, and length of stay among patients with final low glutamine levels

Characteristic	Normal day 6 glutamine levels ($N = 51$)	Low day 6 glutamine levels ($N = 47$)	p value
Number of infected patients	30 (58.8)	38 (80.9)	0.032
Confirmed respiratory tract infection	24 (48.1)	30 (63.8)	0.143
Nosocomial pneumonia	14 (27.5)	22 (46.8)	0.076
Tracheobronchitis	10 (19.6)	8 (17.0)	0.945
Confirmed urinary tract infection	4 (7.8)	1 (2.1)	0.364
Primary bacteremia	9 (17.7)	4 (8.5)	0.301
Other confirmed infections	11 (21.6)	11 (23.4)	0.980
ICU length of stay	9 (6–16)	20 (12–32)	<0.001
Antibiotic used	40 (81.6)	44 (93.6)	0.076
Days of mechanical ventilation	6 (2–12)	15 (8–22)	<0.001
SOFA	4 (3–7)	7 (5–8)	0.007
Hospital length of stay	24 (16–42)	41 (20–64)	0.011
ICU mortality	2 (3.9)	2 (4.3)	0.934
Hospital mortality	3 (5.9)	3 (6.5)	0.952
Glutamine baseline[a]	323 (279–420)	294 (231–370)	0.030
Glutamine day 6[a]	401 (361–482)	284 (244–307)	<0.001
ISS	25 (20–41)	32 (25–50)	0.100
Age (years)	43 (32–59)	38 (27–52)	0.301

Values are numbers of patients (percentages) or median and interquartile range. Confirmed infections were in accordance with Centers for Disease Control definition

SOFA sequential organ failure assessment score, *ISS* injury severity score

[a] Normal range of plasma glutamine measured by HPLC (335–635 μmol/L)

effect on the specified outcomes (infections, length of stay, and mortality).

We also evaluated those patients with low plasma levels of glutamine at two points: before randomization (Table 4) and at the end of the treatment at day 6 (Table 5). Basal low glutamine levels were not associated with any effect on the outcomes (Table 4). Nevertheless, low glutamine levels at day 6 were associated with increased numbers of infected patients (58.8 vs. 80.9 %; $p = 0.032$), longer ICU length of stay (9 vs. 20 days; $p < 0.01$), and longer hospital length of stay (24 vs. 41 days; $p = 0.01$) (Table 5). There were no statistically significant differences regarding mortality.

Discussion

This was a prospective, randomized, double-blind, multicenter trial that investigated i.v. glutamine

supplementation in trauma ICU patients. The main findings of this study were (1) there was no effect of i.v. glutamine supplementation in any of the outcome endpoints measured; (2) the i.v. glutamine supplementation (0.5 g/kg body weight/day of the dipeptide during 5 days) was not enough to normalize the plasma glutamine levels in all patients; (3) low plasma glutamine levels at day 6 were associated with a worse outcome.

In the present study, inclusion was not restricted to patients on PN, which has been the case in other studies. Therefore the study design makes the results representative for a broad range of trauma patients. The high rate of patients included augmented the external validity. Also, the strengths of this study include the randomized and blinded design, rigorous determination of infections, and intention to treat analysis, all of which increase the internal validity of the trial.

The main objective of this trial was to better define the group of trauma patients admitted to the ICU that could benefit from i.v. glutamine supplementation. Compared to the data obtained from the national infection surveillance in Spain [36, 37], the patients included in our study had more infections (62 vs. 20 %), longer ICU length of stay (14 vs. 11 days), and lower ICU mortality (4 vs. 10 %). The higher rate of infections could be explained by the fact that both groups of patients were different because we did not randomize those patients who were not expected to be in the ICU for more than 48 h (owing to imminent death or because they were transferred to the ward), and maybe because the early use of total PN in almost 40 % of our patients in an effort to achieve the nutritional aim. On the other hand, more patients presented infections; therefore, from a theoretical point of view, any difference due to the treatment could be identified easier.

One important aspect of our study is that we monitored the plasma glutamine levels in 100 patients. Interestingly, at the end of the treatment (day 6) 39 % of the patients who received the dipeptide maintained low glutamine levels. American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines [38] state that "when total PN is used in the critical care setting, consideration should be given to supplementation with parenteral glutamine at a dose of 0.5 g/kg/day". The ESPEN guidelines [33] concur with the Canadian guidelines in the dose of glutamine (0.2–0.4 g/kg/day). Our trial provided glutamine supplementation within the recommended dose range, nevertheless it was insufficient in many patients to normalize the levels of glutamine, and this could be one of the reasons that could explain the lack of effect of i.v. glutamine supplementation.

Finally, it is known that low plasma glutamine levels have been associated with increased mortality [9]. In our study we have also described this association on the 6th day after trauma, but not before randomization. The fact that in those patients with higher ISS it was more difficult to achieve normal glutamine levels and that glutamine supplementation in the patients with an ISS greater than 24 points did not have a significant effect on the outcome suggests that a low glutamine level can be considered as a biomarker rather than a factor that should be supplemented. Nevertheless, because we could not normalize the glutamine levels at day 6 in all the patients in the treatment group, this study does not help to clarify this issue. Because the form of the dipeptide employed (L-alanyl-L-glutamine) and the dose used in this trial follow contemporary recommendations, we can only speculate that maybe 5 days is a short period of time to normalize the glutamine levels or maybe that a persistent aggression that perpetuates the low glutamine levels occurs. Future studies should ensure that the plasma glutamine levels in the treated patients are normalized.

Limitations of the study

The protocol involved only 5 days of supplementation in all patients, independently of the type of artificial nutrition required. So it could be argued that the dose of glutamine was suboptimal and that the patients did not present a conditional deficiency. For this reason we measured the levels of glutamine before and after the 5 days of treatment, in an effort to identify those patients with a glutamine deficiency and to ensure the correct amount of glutamine supplementation. Also, owing to licensing restrictions in Spain, we could not provide more than a 9-day supply of glutamine. Other explanations for the lack of effect besides an underdosage (because of a low dose administration or a short period of time for the replacement) could be an inaccurate timing of administration because in both groups the time from injury to initiating the infusion was around 28 h. We therefore cannot rule out that starting the treatment earlier would have a beneficial effect.

As in many parts of the world, nutritional support in Spain is not individualized for each patient to the exact protein and calorie requirement calculated from basal metabolic rate, although individually optimized energy supplementation could reduce nosocomial infections [39]. Although the design of this study was done to meet average estimated requirements for most patients, we did not record how fast the nutrition aim was achieved. It could be possible that some patients did not even achieve the nutritional requirements as occurred in Heyland et al.'s study [18]. Nevertheless we believe that both groups were equally affected by this nutrition approach, which reflects clinical practice in most critical care units. The trial followed routine clinical practices and despite some variations between unit procedures and that the choice between enteral and PN was left to the attending physician's discretion, these data indicate that this study has strong external validity and generalizability of results.

Some other important variables such as number of ventilator-free days, number of antibiotic-free days, or number of ICU-free days were not recorded. Instead we presented the number of days of mechanical ventilation, the number of patients who received antibiotics, and the ICU length of stay. Nevertheless both groups were well matched and we do not believe that these variables, presented in a different manner, would be different in both groups and could mask any treatment effect.

Finally new infections were recorded for only the first 14 days. The intervention was set to 5 days, on the basis of previous trials and recommendations, and it was considered that a longer lasting effect of the trial intervention was unlikely to be evident.

Conclusions

This trial showed that there was no evidence of benefit with i.v. L-alanyl-L-glutamine dipeptide supplementation (0.5 g/kg body weight/day of the dipeptide) during 5 days in trauma patients admitted to the ICU. Future research should confirm or refute that a longer administration could represent any benefit to these patients. Such studies should ensure that the plasma glutamine levels in the treated patients are normalized.

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