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ORIGINAL ARTICLE

Effect of the route of nutrition and L-alanyl-L-glutamine supplementation in amino acids' concentration in trauma patients

J. M. Raurich[1] · J. A. Llompart-Pou[1,2] · A. García-de-Lorenzo[3] · A. Buño Soto[4] · P. Marsé[1] · G. Frontera[2] · J. Pérez-Bárcena[1,2]

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Abstract
Purpose Our purpose was to assess the amino acids' (AAs) profile in trauma patients and to assess the effect of the route of nutrition and the exogenous ALA-GLN dipeptide supplementation on plasma AAs' concentration.
Methods This is a secondary analysis of a previous randomized controlled trial. On day 1 and day 6 after trauma, plasma concentration of 25 AAs was measured using reverse phase high-performance liquid chromatography. Results were analyzed in relation to the route of nutrition and supplementation of ALA-GLN dipeptide. Differences between plasma AAs' concentrations at day 1 and day 6 were evaluated using the Student's *t* test or Mann–Whitney–Wilcoxon test. One-way ANOVA and the Kruskal–Wallis test were used to compare groups. A two-sided *p* value less than 0.05 was considered statistically significant.
Results Ninety-eight patients were analyzed. Mean plasma concentrations at day 1 were close to the lower normal level for most AAs. At day 6 we found an increase in the eight essential AAs' concentrations and in 9 out of 17 measured non-essential AAs. At day 6 we found no differences in plasma concentrations for the sum of all AAs ($p = .72$), glutamine ($p = .31$) and arginine ($p = .23$) distributed by the route of nutrition. Administration of ALA-GLN dipeptide increased the plasma concentration of alanine ($p = .004$), glutamine ($p < .001$) and citrulline ($p = .006$).
Conclusions We found an early depletion of plasma AAs' concentration which partially recovered at day 6, which was unaffected by the route of nutrition. ALA-GLN dipeptide supplementation produced a small increase in plasma levels of glutamine and citrulline.

Keywords Amino acids · Severe trauma · Glutamine · Nutrition

✉ J. M. Raurich
joan.raurich@ssib.es

J. A. Llompart-Pou
juanantonio.llompart@ssib.es

A. García-de-Lorenzo
agdl@telefonica.net

A. Buño Soto
abuno.hulp@salud.madrid.org

P. Marsé
pmarse@telefonica.net

G. Frontera
guillem.frontera@ssib.es

J. Pérez-Bárcena
juan.perez@ssib.es

1 Servei de Medicina Intensiva, Hospital Universitari Son Espases, Carretera Valldemossa, 79, 07010 Palma de Mallorca, Illes Balears, Spain

2 Instituto de Investigación Sanitaria de Palma (IdISPa), Palma de Mallorca, Spain

3 Servicio de Medicina Intensiva, Hospital Universitario La Paz/Carlos III, IdiPAZ, Madrid, Spain

4 Laboratory Medicine Department, Hospital Universitario La Paz/Carlos III, IdiPAZ, Madrid, Spain

Introduction

Multiple trauma and sepsis are associated with a notably early depletion of plasma amino acids' (AAs) concentrations or hypoaminoacidemia [1–7]. The underlying causes of hypoaminoacidemia include, but are not limited to, increased hepatic uptake of gluconeogenic AAs [8], increased loss of AAs by urine or hyperaminoaciduria [4], persistence of hypermetabolism [9, 10], inadequacy of protein and calorie

intakes [11], loss of AAs by blood loss and hemodilution secondary to resuscitation with positive fluid balance [12, 13].

Another potential cause that may affect the plasma AAs' concentration in critically ill patients is the route of artificial nutrition used, whether enteral, parenteral or both, as it has been demonstrated for some AAs such as glutamine, citrulline and arginine [12, 14, 15]. In addition, the route of nutrition determines differences in their respective formula compositions (peptides in enteral nutrition vs. AAs in parenteral nutrition) and in the complexity of the metabolic process of AAs [2, 16].

The exogenous administration of L-alanyl-L-glutamine dipeptide (ALA-GLN dipeptide) increases the plasma concentration of glutamine and serves as a substrate for intestinal L-citrulline production and renal L-arginine synthesis in patients without acute kidney injury [14, 15, 17–19]. The main goal of the exogenous administration of ALA-GLN dipeptide is the reduction of infections in critically ill patients, since it has been proven to enhance the immune system [20–22]. However, several trials failed to demonstrate any clinical beneficial effect with artificial nutrition supplemented with ALA-GLN dipeptide in critically ill patients [23–25].

The aims of this study were to assess the AAs' profile in trauma patients and to evaluate the effect of the route of nutrition and the exogenous ALA-GLN dipeptide supplementation on the plasma concentration of AAs, with special focus on those related to glutamine metabolism.

Materials and methods

This was a secondary analysis of a previously published randomized controlled trial [25], which was conducted 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. The original trial was supported by a grant from the *Ministerio de Sanidad y Consumo* of Spain and was registered at ClinicalTrials.gov as NCT01250782.

Patients

This sub-study included 100 out of 142 critically ill trauma patients of the original study [25]. These 100 patients were included in the coordinating center of the study and blood samples were taken to determine the plasma concentration of AAs.

Eligible patients satisfied the following criteria: adult patients 18 to 75 years old, admitted to the Intensive Care Unit (ICU) with a diagnosis of trauma and an injury severity score ≥ 10 points, requiring enteral nutrition, parenteral nutrition or both, with expected length of stay in the ICU at least 48 h and written informed consent from patients or closest relative. The exclusion criteria included significant hepatic failure (patients with Child C cirrhosis), severe renal failure (glomerular filtration less than 25 mL/min), pregnancy, weight greater than 110 kg, or being 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 and adapted by the Spanish National Society of Intensive Care Medicine [26]. Nutritional support was based on contemporary guidance from the European Society for Clinical Nutrition and Metabolism (ESPEN) [27]. Specific details of sedatives used, nutritional target and protocol and ALA-GLN dipeptide randomization have been published elsewhere [25].

Amino acid analysis

On day 1 and day 6 after trauma, from 08:00 to 10:00 AM, blood samples were drawn from arterial lines and collected in heparin tubes, which were directly put on ice. Within 10–15 min after collection, samples were centrifuged for 10 min at 2500 rcf at 4 °C. Two portions of 500 µL plasma of each sample were put in two cryovials with 20 mg dry sulfosalicylic acid for deproteinization, and then vortexed, frozen in liquid nitrogen, and kept at − 80 °C until analysis. Then, plasma concentration of the 25 AAs was measured using reverse phase high-performance liquid chromatography (HPLC).

Data collection

We collected demographic characteristics, including age, gender and weight, severity of illness by the Injury Severity Score (ISS) and the Sepsis-related Organ Failure Assessment (SOFA) score calculated after the first 24 h of ICU stay, the type of trauma and the route of artificial nutrition. Plasma AAs' concentrations were measured at day 1 and day 6 after trauma. Length of mechanical ventilation, ICU and in-hospital length of stay, and ICU and in-hospital mortality were also recorded.

Statistical analysis

Categorical data are presented as number (percentage). Continuous variables are presented as mean and standard deviation (SD) or as median and interquartile range (IQR) where appropriate. Differences between plasma AAs' concentrations at day 1 and day 6 were evaluated using the Student's

t test or Mann–Whitney–Wilcoxon test as appropriate. One-way ANOVA and the Kruskal–Wallis test were used to compare groups. A two-sided *p* value of less than 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics version 20.0.

Results

We analyzed 25 AAs in 100 trauma ICU patients. Two patients were excluded from the final analysis because AAs were only measured at day 1 (Fig. 1). The most common type of injury was traumatic brain injury, which was present in 74.5% of the patients (Table 1). The route of nutrition was enteral (55.1%), enteral supplemented parenteral (32.7%) and parenteral (12.2%) (Table 1). In-hospital mortality was 6.1%.

Plasma AAs' concentration at day 1 and day 6

Mean plasma concentrations at day 1 were close to the lower normal level for most AAs (Table 2). At day 6 we found a statistical significant increase in the 8 essential AAs' concentrations and in 9 out of 17 measured non-essential AAs (Table 2). The increase in AAs at day 6 was not significant for alanine, argininosuccinic acid, citrulline, glutamine, glycine, histidine, hydroxyproline and taurine (Table 2). The sum of total AAs ($p < .001$), essential AAs ($p < .001$), non-essential AAs ($p = .003$), branched-chain AAs (BCAAs) ($p < .001$) and aromatic AAs (AAAs) ($p < .001$) showed a significant increase at day 6 when compared to day 1 concentrations (Fig. 2).

Effect of the route of nutrition on plasma AAs' concentration

At day 1 (prior initiating artificial feeding) we found no differences in plasma concentrations for the sum of all AAs ($p = .42$), glutamine ($p = .52$), citrulline ($p = .29$) and arginine ($p = .50$) distributed by the route of nutrition (Fig. 3). At day 6 we found no differences in plasma concentrations for the sum of all AAs ($p = .72$), glutamine ($p = .31$) and arginine ($p = .23$) distributed by the route of nutrition (Fig. 3).

At day 6 of the trauma and compared to day 1 values, we found a significant increase in the concentration of the sum of all AAs and arginine for each of the routes of nutrition (Fig. 3). Plasma concentration of citrulline increased significantly at day 6 only in the group of enteral nutrition

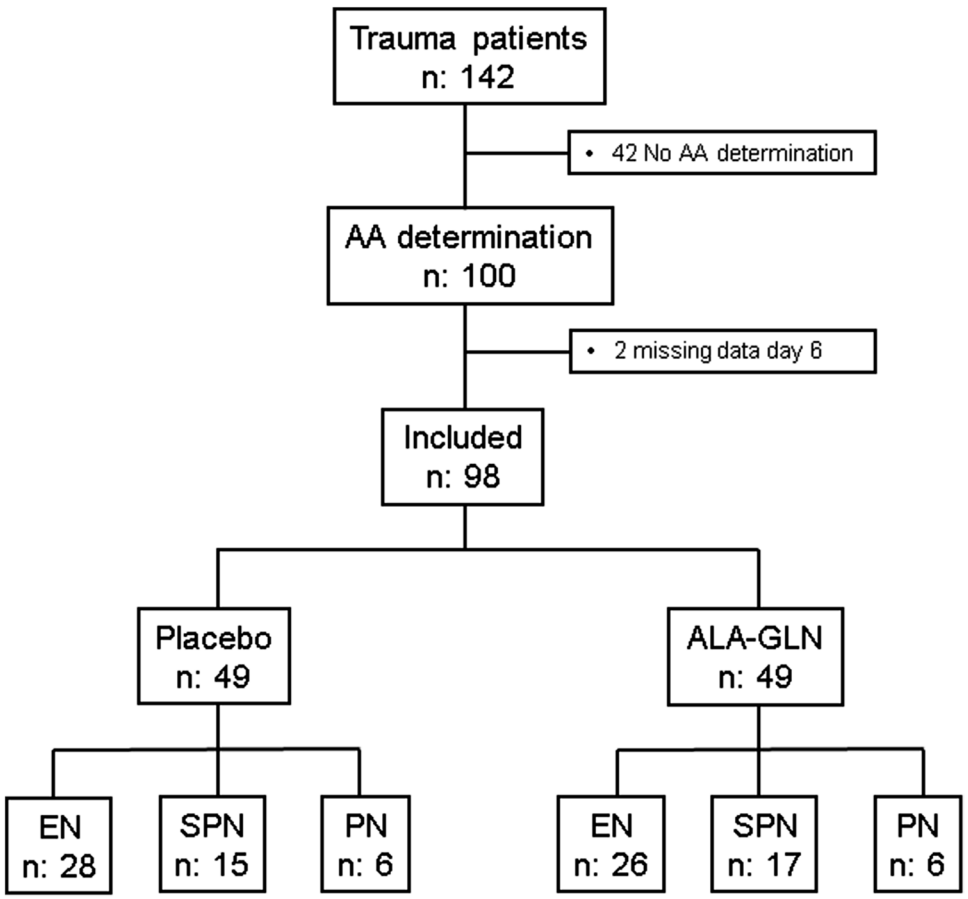

Fig. 1 Flowchart of patients included in the study distributed by having received L-alanyl-L-glutamine dipeptide supplementation and by the route of nutrition. *AA* amino acid, *ALA-GLN* L-alanyl-L-glutamine dipeptide. *EN* enteral nutrition, *SPN* supplemented parenteral nutrition, *PN* parenteral nutrition

Table 1 Clinical characteristics of the 98 trauma patients included in the study

Variable	Value
Gender female, *n* (%)	13 (13.3)
Age, years, mean (SD)	43 (17)
Weight, Kg, mean (SD)	79 (12)
Type of trauma, *n* (%)	
Thoracic trauma	58 (59.2)
Abdominal trauma	16 (16.3)
Pelvic trauma	48 (49.0)
Spinal cord trauma	15 (15.3)
Severe TBI	39 (39.8)
Moderate TBI	34 (34.7)
Hemorrhagic shock, *n* (%)	15 (15.3)
Injury severity score, median (IQR)	29 (25–41)
SOFA score, median (IQR)	7 (4–8)
Route of nutrition, *n* (%)	
Enteral	54 (55.1)
Supplemented parenteral	32 (32.7)
Parenteral	12 (12.2)
Duration of mechanical ventilation, days, median (IQR)	10 (4–19)
ICU length of stay, days, median (IQR)	14 (7–24)
In-hospital length of stay, days, median (IQR)	29 (17–50)
ICU mortality, *n* (%)	4 (4.1)
In-hospital mortality, *n* (%)	6 (6.1)

TBI traumatic brain injury, *SOFA* sepsis-related organ failure assessment, *ICU* Intensive Care Unit

($p = .03$) (Fig. 3). No differences were found for glutamine concentrations between day 1 and day 6 distributed by the route of nutrition (Fig. 3).

Effect of ALA-GLN dipeptide supplementation on plasma AAs' concentration

We found no differences in the plasma concentration of alanine ($p = .73$), glutamine ($p = .55$), citrulline ($p = .76$) and arginine ($p = .51$) at day 1 between placebo and ALA-GLN dipeptide groups (Fig. 4). Compared to placebo, exogenous administration of ALA-GLN dipeptide increased the plasma concentration of alanine ($p = .004$), glutamine ($p < .001$) and citrulline ($p = .006$), but no differences were found in arginine levels between placebo and ALA-GLN groups at day 6 ($p = .57$) (Fig. 4).

Discussion

The main results of our study were: (1) a significant early depletion in plasma AAs' concentration occurs after trauma which partially recovers at day 6; (2) we did not find differences in the plasma AAs depending on the route of nutrition at day 6, except for citrulline concentration; and (3) the intravenous infusion of ALA-GLN dipeptide slightly increased the plasma concentration of alanine, glutamine and citrulline at day 6 without differences in arginine concentrations.

The early depletion of plasma AAs' concentration after severe trauma (around 30%) is in accordance to other studies in critically ill trauma patients [1, 4, 6]. This hypoaminoacidemia in critically ill trauma patients relies on different mechanisms, such as reduced rates of appearance of plasma AAs (reduced protein intake) [11] and increased disappearance of AAs from plasma (increased hepatic uptake of gluconeogenic AAs, hiperaminoaciduria and blood loss) [4, 8].

The later increase in the concentration of AAs at day 6 can be attributed to the nutritional contribution of peptides and/or AAs delivery by enteral/parenteral routes and from muscle proteolysis with protein breakdown and AAs release, in particular BCAAs [16]. Thus, in our study cohort we found an increase of 23% in the plasma concentration of AAs measured, with an increase of 43% in the concentrations of BCAAs (isoleucine, leucine, and valine), similar to Parent et al.'s [6] study with critically ill trauma patients. The increase in BCAAs after trauma or sepsis is considered specific to proteolysis [16]. Based on its potential neuroprotective role, BCAAs' supplementation constitutes an appealing target in trauma patients, especially in those with severe head injury [28].

We found no differences in the concentration of AAs depending on the route of nutrition used. This was not surprising because when enteral and parenteral nutrition are closely matched for energy and proteins, both can result in similar profiles for most plasma AAs [29]. In our study, at ICU admission the nutritional target for all admitted patients was a caloric intake of 28 kcal/kg/day and protein of 1–2 g/kg/day, independent of the route of nutrition used.

Citrulline has been postulated as a biomarker reflecting enterocyte function in critically ill patients [30, 31]. Accordingly, we have observed a lower plasma concentration of citrulline in patients with enteral supplemented parenteral nutrition and parenteral nutrition. In adult patients, glutamine, glutamate, proline and ornithine may be utilized for citrulline synthesis in the gut with posterior synthesis of arginine in the kidney [32], being glutamine the main contributor up to 80% of citrulline [33].

We found a remarkably significant depletion of plasma alanine, glutamine, citrulline and arginine after trauma at day 1, similar to previous reports that described declines nearly 40–50% in trauma patients [34–36]. However, supplementation with ALA-GLN dipeptide to half of the patients resulted in a median increase of only 20% of alanine, glutamine and citrulline. In opposition, the median plasma concentration of arginine increased at day 6 significantly up

Table 2 Amino acids delivered in route of nutrition, normal range of plasma amino acids concentration, and plasma amino acids' concentrations at day 1 and day 6 after trauma

	PN	EN	Normal range (µmol/L)	Day 1 (µmol/L)	Day 6 (µmol/L)	*p* value
Essential						
Isoleucine	x	x	33–100	46 (31–64)	73 (64–90)	< .001
Leucine	x	x	55–175	105 (79–139)	153 (132–190)	< .001
Lysine	x	x	80–260	91 (69–112)	144 (117–176)	< .001
Methionine	x	x	10–40	18 (14–24)	27 (22–35)	< .001
Phenylalanine	x	x	30–110	54 (45–62)	68 (58–79)	< .001
Threonine	x	x	60–175	66 (51–84)	98 (80–113)	< .001
Tryptophan	x	x	25–75	32 (26–40)	37 (28–45)	.002
Valine	x	x	135–330	203 (162–252)	295 (256–348)	< .001
Non-essential						
Alanine	x	x	150–515	236 (177–319)	257 (212–316)	.13
Arginine	x	x	75–175	53 (45–67)	103 (83–118)	< .001
Argininosuccinic acid			4–13	5.7 (4.9–7.6)	6.5 (5.4–8.2)	.20
Asparagine		x	35–135	43 (32–57)	56 (44–76)	< .001
Aspartic acid		x	6–22	3.1 (2.2–5.4)	5.5 (4.0–8.6)	< .001
Citruline			14–40	13.8 (11.2–16.5)	14.8 (11.1–18.1)	.20
Cystine		x	15–55	8.6 (5.6–13.7)	12.2 (7.3–18.7)	< .001
Glutamic acid/glutamate		x	25–110	43 (33–63)	53 (39–72)	.008
Glutamine[a]		x	335–635	311 (256–400)	338 (283–402)	.44
Glycine		x	80–280	112 (92–140)	124 (100–159)	.41
Histidine	x	x	20–80	48 (41–61)	47 (40–52)	.08
Hydroxyproline	x		5–30	5.3 (3.9–7.6)	5.0 (4.1–7.0)	.50
Ornithine			25–100	29 (23–40)	55 (42–67)	< .001
Proline	x	x	110–260	132 (104–187)	215 (166–279)	< .001
Serine	x	x	60–180	56 (43–68)	77 (59–92)	< .001
Taurine	x		40–175	44 (29–59)	43 (27–61)	.76
Tyrosine	x	x	40–90	49 (42–60)	62 (53–79)	< .001

PN parenteral nutrition, *EN* enteral nutrition, *x* amino acid in the nutrition

[a]L-Alanyl-L-Glutamine dipeptide supplementation in 49 patients

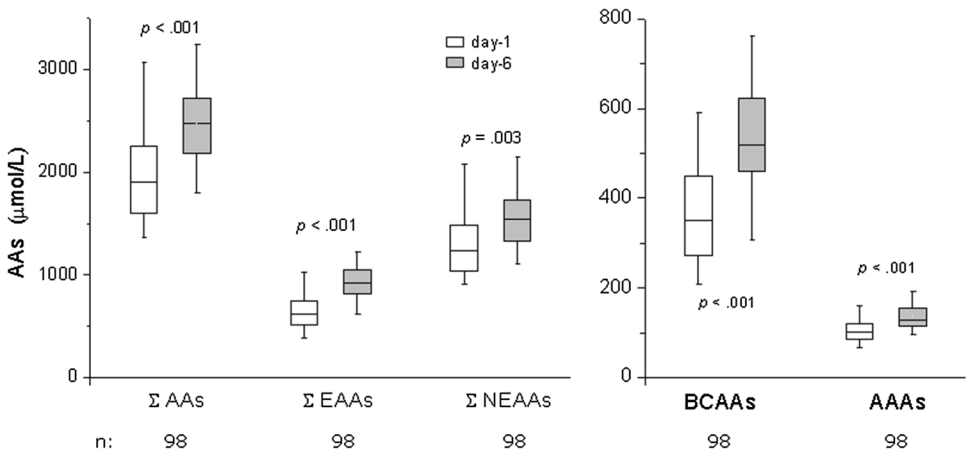

Fig. 2 Plasma concentration of the sum of all amino acids (∑ AAs), essentials amino acids (∑ EAAs), non-essential amino acids (∑ NEAAs), branched-chain amino acids (BCAAs) and aromatic amino acids (AAAs) at day 1 (white boxes) and day 6 (gray boxes). The horizontal lines within the boxes indicate medians, the lower and upper ends of the boxes the 25th and 75th percentiles, respectively, and the I bars the 5th and 95th percentiles. *n* indicates the number of patients in each group

to 100% being supplemented or not with ALA-GLN dipeptide. The lack of differences in the concentration of arginine between both groups would rely on the fact that plasma citrulline is a precursor of only 10% of the plasma arginine [33], and due to the supply of arginine within nutrition and arginine production from protein breakdown [35]. Our

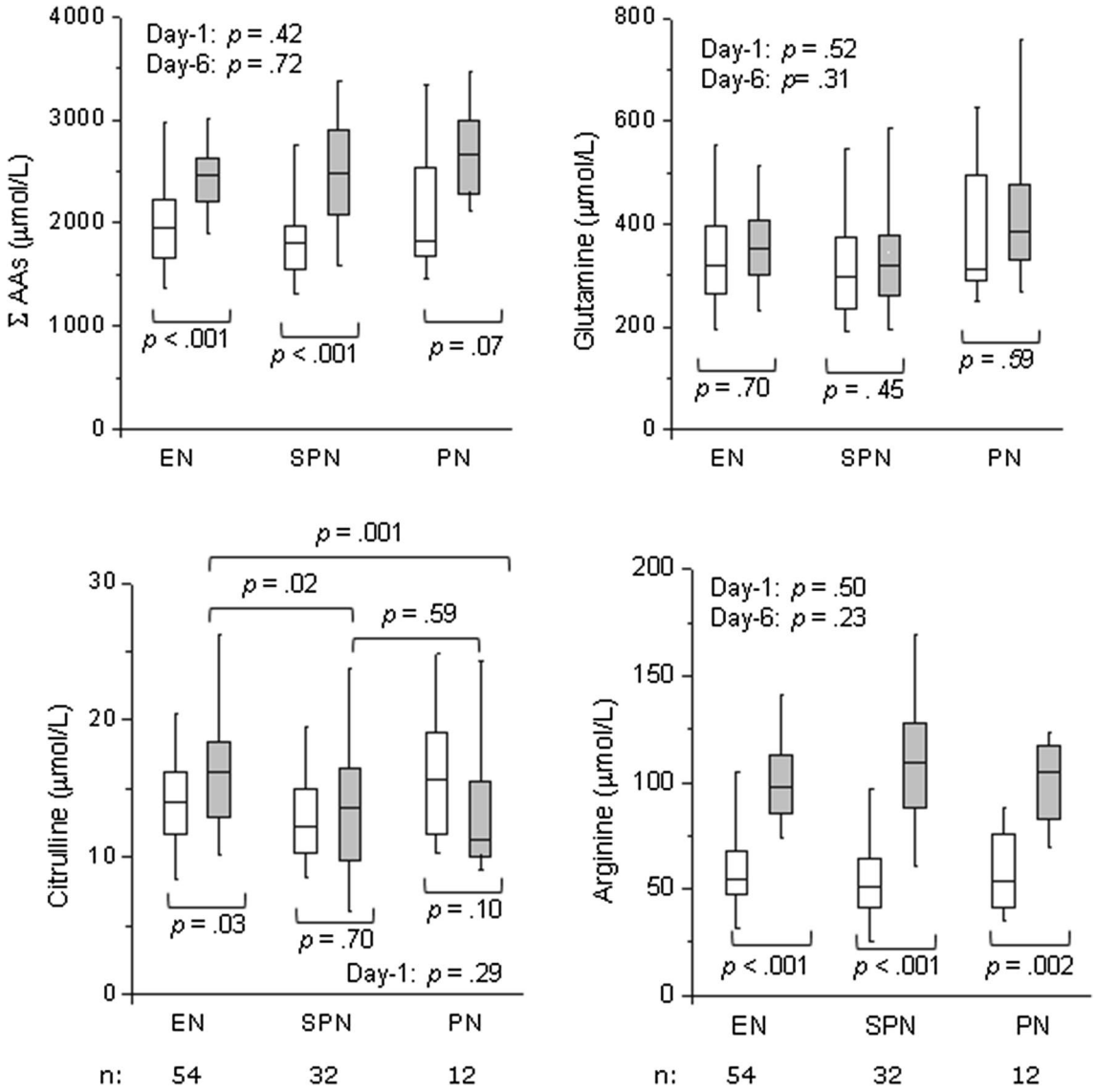

Fig. 3 Plasma concentration of the sum of all amino acids ($\sum$ AAs), glutamine, citrulline, and arginine at day 1 (white boxes) and day 6 (gray boxes) according to the route of nutrition: enteral nutrition (EN), enteral nutrition supplemented with parenteral nutrition (SPN), and parenteral nutrition (PN). The horizontal lines within the boxes indicate medians, the lower and upper ends of the boxes the 25th and 75th percentiles, respectively, and the I bars the 5th and 95th percentiles. *n* indicates the number of patients in each group

results were in accordance with other studies that suggested that the increase in arginine was independent of the route of nutrition and ALA-GLN dipeptide supplementation when these critically ill patients are adequately fed [12, 29, 37].

Considering that immunonutrition may decrease infectious complication rates in elective surgery [38] and that septic patients have low plasma concentrations of glutamine, cirtrulline and arginine [39], supplementing nutrition with immunonutrients such as glutamine or arginine in severe trauma patients to reduce the rate of infection is appealing. However, Vermeulen et al. [37] using isotopes tracers of glutamine, citrulline and arginine did not demonstrate a significantly higher turnover of glutamine into the substrates citrulline and arginine in critically ill patients receiving enteral nutrition. This can explain the weak increase in glutamine concentration in the group of patients supplemented with the ALA-GLN dipeptide and the similar increase in the concentration of arginine in both groups and even may play a role in the lack of beneficial effects of supplementation with ALA-GLN dipeptide to prevent infection in our original study [25]. Whether supplementing a higher dose of ALA-GLN would result in similar findings remains to be determined.

Some limitations must be acknowledged in our secondary analysis: the choice between enteral, parenteral nutrition or a combination of both was left to the attending physician

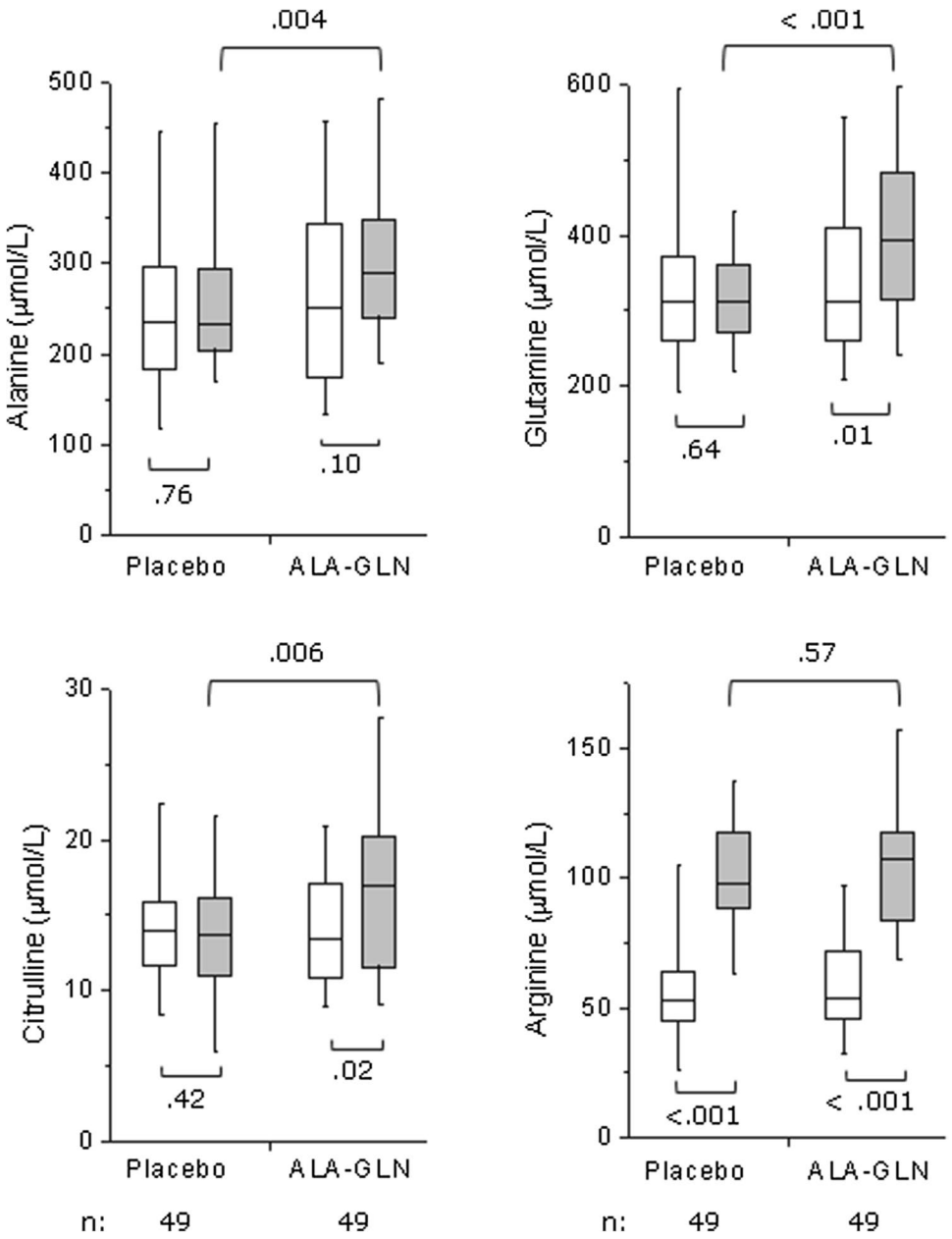

Fig. 4 Plasma concentration of alanine, glutamine, citrulline and arginine at day 1 (white boxes) and day 6 (gray boxes) according to group without (placebo) and with L-alanyl-L-glutamine dipeptide supplement (ALA-GLN). The horizontal lines within the boxes indicate medians, the lower and upper ends of the boxes the 25th and 75th percentiles, respectively, and the I bars the 5th and 95th percentiles. *n* indicates the number of patients in each group

discretion. In addition, we did not record the caloric and protein intake and protein loss in the feces of each patient. The degree of absorption for enteral protein is a complicated factor since it may be variable, and diarrhea, which is often neglected in daily ICU practice, results in potentially important energy and protein losses [40]. Moreover, the plasma concentration of AAs constitutes a small and rapidly changing pool that conforms only 10% of the total free AA pool [13]. Therefore, changes in plasma AAs should be interpreted with caution.

In conclusion, after severe trauma there was an early depletion in the plasma AAs' concentration which partially recovered at day 6. The route of nutrition did not affect the plasma AAs' concentration. Nutrition supplemented with ALA-GLN dipeptide produced a small increase in plasma levels of glutamine and citrulline without direct effect on arginine concentration.

Compliance with ethical standards

Conflict of interest Llompart-Pou JA, Raurich JM, Buño Soto A, Frontera G, Pérez-Bárcena J declare no conflict of interest. García-de-Lorenzo A and Marsé P declare having received speaking honoraria from Fresenius Kabi.

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