Parenteral administration of different amounts of branch-chain amino acids in septic patients: Clinical and metabolic aspects

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Abstract
Objective: To study the effects of a total parenteral nutrition solution changing branch-chain amino acid concentrations and/or nitrogen supply on protein metabolism, length of stay, and mortality rate; and to evaluate the unique metabolic status of sepsis that leads to a search for specific total parenteral nutrition formulas.

Design: Prospective, randomized, and multicenter study.

Setting: Intensive care units (ICUs) in seven university hospitals.

Patients: Sixty-nine septic patients.

Measurements and Main Results: The patients were randomized into three groups according to the total parenteral nutrition administered. Group A (n = 22) and B (n = 25) patients received 1.5 g of amino acids/kg/day with a nonprotein ratio of 100:1 calories/g of nitrogen, and a varying branch-chain amino acids percentage (group A [23%]; group B [45%]). Group C patients were treated with 1.1 g/kg/day of amino acids with a nonprotein ratio of 140:1 calories/g of nitrogen and 45% branch-chain amino acids. All diets were isocaloric. Prealbumin, retinol-binding protein, nitrogen balance, and plasma amino acid profiles (24 amino acids) were determined at baseline and after 3, 7, and 11 days of total parenteral nutrition. The length of stay in the ICU was recorded.

At baseline (preparenteral nutrition), no differences in age, gender, severity of the condition, or clinical chemistry were found between the groups. Prealbumin and retinol-binding protein increased in groups B (p < .004, p < .002, respectively) and C (p < .001, p < .002, respectively). Plasma arginine increased significantly in group C (p < .05), and plasma valine (p < .0001, p < .04, respectively), leucine (p < .005, p < .03, respectively), and isoleucine (p < .001, p < .0001, respectively) increased significantly in groups B and C. The length of stay in the ICU did not change between the groups. The mortality rate in groups B and C was less than in group A (p < .03).

Conclusions: Our results suggest that the branch-chain amino acids-rich formulas (45%) show a beneficial effect in septic patients. Crit Care Med 1997; 25:418-424

Key Words: branch-chain amino acids; sepsis; mortality; glutamine; arginine; prealbumin; retinol-binding protein; parenteral nutrition

Appropriate nutritional support is part of the therapy in septic patients requiring intensive care unit (ICU) care. Altered protein metabolism during injury has been well documented [1-3]. It has been suggested that total parenteral nutrition decreases high muscle protein breakdown and improves impaired body protein synthesis during sepsis [4-6]. The properties of the branch-chain amino acids (valine, leucine, isoleucine) as energy substrates, substrates for gluconeogenesis, and modulators of muscle protein metabolism make the use of branch-chain amino acids-enriched solutions theoretically appropriate for the management of the metabolic alterations that occur in sepsis [7]. The in vitro and in vivo animal data available have suggested a benefit for the branch-chain amino acid on protein synthesis and degradation in sepsis. Branch-chain amino acids-enriched solutions (45%) increase the rate of hepatic protein synthesis and acute-phase proteins in critically ill and septic patients. These proteins may be important in host defense mechanisms against infection. Thus, the administration of solutions containing a high proportion of branch-chain amino acid may improve the chances of survival for such patients via this mechanism [8]. Greater benefits must be shown in man before the use of branch-chain amino acids formulations in sepsis can be endorsed [9-12].
The purpose of the present study was to assess the effectiveness of branch-chain amino acids on protein metabolism, length of stay, and mortality rate in the ICU. The quality and quantity of amino acids administration was varied by using amino acid solutions enriched in branch-chain amino acids in septic patients receiving total parenteral nutrition.

MATERIALS AND METHODS

In a prospective, randomized, multicenter study (seven University hospitals), 69 septic patients unable to receive enteral nutrition by formal contraindication (peritonitis, ileus) were randomized in a centralized way into three different groups (A, B, and C), in relation to the parenteral nutrition administered. The randomization schedule was generated for each center by an external company, using SAS PROC PLAN. The randomization was a blocked randomization scheme in order to preserve balance at any time throughout the study. Adult patients who were considered to be septic, according to the American College of Chest Physicians/Society of Critical Care Medicine septic definition [13], who were in need of parenteral nutrition within the first three days of ICU admission and for at least 11 days, were entered into the study. Severity of illness was assessed by means of the Acute Physiology and Chronic Health Evaluation (APACHE) II score [14]. APACHE II scores were calculated using data gathered during the first 24 hrs of admission. Patients with renal (plasma creatinine of >2 mg/dL) and liver failure (plasma bilirubin of >3 mg/dL) were excluded.

This investigation was approved by the Ethics Committees of our institutions according to the International Declarations of Helsinki and Tokyo and the recommendations of the World Health Organization. Informed consent was obtained from each patient or his/her legal representative for participation in the study.

Each group was infused continuously through a central vein with an isocaloric (24 nonprotein calories/kg/day) parenteral nutrition during 11 days. Nonprotein calories were given as 60% glucose (3.4 g/kg/day) and 40% fat emulsion (1 g/kg/day) (Intralipid® 20%, Pharmacia and Upjohn, Madrid, Spain). The patients in groups A and B received a total amino acid load of 1.5 g amino acids/kg/day with a calories/nitrogen ratio of 100:1; and the patients in group C received 1.1 g amino acids/kg/day with a calories/nitrogen ratio of 140:1. Group A received an amino acid solution with 23% branch-chain amino acids (FreAmine® 10%, Pharmacia and Upjohn), and groups B and C received a solution with 45% branch-chain amino acids (FreAmine 6.9% high branched chain, Pharmacia and Upjohn). Group A received a branch-chain amino acids load of 0.345 g/kg/day; group B received a branch-chain amino acids load of 0.675 g/kg/day, and group C received a branch-chain amino acids load of 0.5 g/kg/day (Table 1). In summary, groups A and B represent standard vs. branch-chain amino acids-supplemented parenteral nutrition, and group C was treated with less nitrogen intake and a higher calories/nitrogen ratio than groups A and B, but a higher branch-chain amino acids load than the standard group (23% branch-chain amino acids). Vitamins, minerals, and trace elements were given in sufficient amounts each day.

Patients underwent clinical and routine chemistry evaluations. Prealbumin and retinol-binding protein, nitrogen balance, and 24 plasma amino acids were measured before (day 0), and after 3, 7, and 11 days of parenteral nutrition. Prealbumin was determined by the kinetic nephelometric method and retinol-binding protein was determined by simple radial immunodiffusion (LC-Partigen Institution plates, Behring, Madrid, Spain). Nitrogen balance was calculated by Lee's modified equation (nitrogen balance = nitrogen intake - nitrogen excretion - nitrogen excretion x 0.56 + 3) [15]. Plasma amino acids were measured using a high-protein liquid chromatography reversed-phase precolumn derivatization (picotag).

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Data were expressed as mean +/- SEM. Statistical significance was determined using one-way analysis of variance and multifactorial analysis of variance for intra-group differences, chi-square test for qualitative variables, and Kaplan-Meier method for analysis of survival. A p < .05 was considered statistically significant. Two statisticians supervised the clinical trial.

RESULTS
The study groups are described in Table 2. There were no significant differences in age and gender, nor in the APACHE II score and mean predicted mortality rate (28 +/- 16%), inotropic support, or sepsis etiology between the groups (Table 3). Group B had three more patients than groups B and C because these three patients died after randomization and before the beginning of the clinical trial. There were no errors in randomization nor protocol violations.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age (yr)</th>
<th>Gender (M/F)</th>
<th>APACHE II</th>
<th>Mechanical Ventilation (%)</th>
<th>Inotropic Drugs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>22</td>
<td>51.8 ± 4</td>
<td>13/9</td>
<td>17.7 ± 1</td>
<td>69.6</td>
<td>47.8</td>
</tr>
<tr>
<td>B</td>
<td>25</td>
<td>60.8 ± 4</td>
<td>14/11</td>
<td>15.7 ± 1.6</td>
<td>73.1</td>
<td>46.2</td>
</tr>
<tr>
<td>C</td>
<td>22</td>
<td>49.5 ± 4</td>
<td>15/7</td>
<td>17.1 ± 0.9</td>
<td>42.9*</td>
<td>33.3</td>
</tr>
</tbody>
</table>

**APACHE II, Acute Physiology and Chronic Health Evaluation II**; Group A, patients receiving 1.5 g of amino acids/kg/day, with a nonprotein ratio of 100:1 calories/g of nitrogen and 23% branch-chain amino acids; Group B, patients receiving 1.5 g of amino acids/kg/day, with a nonprotein ratio of 100:1 calories/g of nitrogen and 45% branch-chain amino acids; Group C, patients receiving 1.1 g/kg/day of amino acids, with a nonprotein ratio of 140:1 calories/g of nitrogen and 45% branch-chain amino acids.

*p = NS; 'p < .046.

**Table 2.** Patient population (mean +/- SEM)

**Table 3.** Sepsis etiology

At baseline, no significant differences were observed between the groups. Vital signs varied according to the individual patient's state of metabolic stress. No abnormalities in vital signs could be attributed to the parenteral nutrition solution. No differences in inotropic drugs or mechanical ventilation requirements were observed between the groups during the study period. The liver function test showed a statistically significant increase in gamma glutamyltransferase in group B (from 76 +/- 26 to 199 +/- 46 IU/L, p < .05) and an increase in alkaline phosphatase in group C (from 174 +/- 17 to 332 +/- 52 IU/L, p < .05). There were no intergroup differences for the liver function test. Decreased plasma albumin concentrations were observed at the beginning of the study and remained unchanged during the study period in all of the groups. There were no differences in albumin and plasma substitutes administered between the groups.

At the beginning of the study, all of the groups showed diminished plasma prealbumin concentrations. In group A, the values remained decreased throughout the study, but in group B (p < .004), and more significantly in group C (p < .001), the plasma prealbumin concentrations increased during the study period. Retinol-binding protein behaved the same as plasma prealbumin (Table 4). Initially, all of the patients showed low plasma values, with plasma protein concentrations increasing significantly in groups B and C during the study period.
Group A, patients receiving 1.5 g of amino acids/kg/day, with a nonprotein ratio of 100:1 calories/g of nitrogen and 23% branch-chain amino acids; Group B, patients receiving 1.5 g of amino acids/kg/day, with a nonprotein ratio of 100:1 calories/g of nitrogen and 45% branch-chain amino acids; Group C, patients receiving 1.1 g/kg/day of amino acids, with a nonprotein ratio of 140:1 calories/g of nitrogen and 45% branch-chain amino acids.

Table 4. Plasma prealbumin and retinol-binding protein (RBP) (mean +/- SEM)

<table>
<thead>
<tr>
<th>Day</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8.7 ± 1.3</td>
<td>8.8 ± 0.7</td>
<td>8.7 ± 0.7</td>
</tr>
<tr>
<td>3</td>
<td>9.6 ± 1.1</td>
<td>10.6 ± 1.1</td>
<td>10 ± 0.9</td>
</tr>
<tr>
<td>7</td>
<td>11.4 ± 1.3</td>
<td>15.8 ± 2.0</td>
<td>14.6 ± 1.3</td>
</tr>
<tr>
<td>11</td>
<td>12 ± 1.7</td>
<td>12.7 ± 1.3</td>
<td>16 ± 1.5</td>
</tr>
</tbody>
</table>

Group A, B, C: p < .0001

All groups of patients started the study with a very negative nitrogen balance (group A [-15.9 ± 1.8], group B [-13.2 ± 1.2], and group C [-17.3 ± 1.4 g/day]), which improved significantly over baseline values during subsequent study days in all of the groups studied; however, no positive nitrogen balance was obtained after 11 days of parenteral nutrition. There was no correlation between the branch-chain amino acid load administered and improvement in nitrogen balance, and results showed no statistical significance in nitrogen balance evolution (Table 5).

Table 5. Nitrogen balance (g/day) (mean +/- SEM)

<table>
<thead>
<tr>
<th>Day</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-15.9 ± 1.8</td>
<td>-13.2 ± 1.2</td>
<td>-17.3 ± 1.4</td>
</tr>
<tr>
<td>3</td>
<td>-6.7 ± 1.8</td>
<td>-5.4 ± 1.6</td>
<td>-6.7 ± 1.1</td>
</tr>
<tr>
<td>7</td>
<td>-8.8 ± 1.5</td>
<td>-4.1 ± 1.6</td>
<td>-4.2 ± 1.5</td>
</tr>
<tr>
<td>11</td>
<td>-2.5 ± 1.8</td>
<td>-5.8 ± 2.6</td>
<td>-6.9 ± 1.8</td>
</tr>
</tbody>
</table>

Group A, B, C: p < .03

Plasma concentrations of all three branch-chain amino acids increased (p < .05) during the study period in groups B and C (Table 6).

Table 6. Branch-chain amino acids (mean +/- SEM)

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucine (65-175 μmol/L)</td>
<td>108.9 ± 14.5</td>
<td>113.8 ± 14.8</td>
<td>133.4 ± 11.2</td>
</tr>
<tr>
<td>Day 0</td>
<td>121.2 ± 14.4</td>
<td>203 ± 13.1</td>
<td>192.9 ± 18.4</td>
</tr>
<tr>
<td>Day 3</td>
<td>117.6 ± 9.3</td>
<td>185.6 ± 22.7</td>
<td>190 ± 19.2</td>
</tr>
<tr>
<td>Day 7</td>
<td>121.1 ± 20.9</td>
<td>240.7 ± 64.4</td>
<td>194.4 ± 21.5</td>
</tr>
<tr>
<td>Day 11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p Value</td>
<td>NS</td>
<td>&lt;.005</td>
<td>&lt;.03</td>
</tr>
</tbody>
</table>

Isoleucine (35-100 μmol/L) | 51 ± 5.3 | 59 ± 11.3 | 59 ± 3.6 |
| Day 0 | 97.3 ± 9.5 | 135.9 ± 10.7 | 90.5 ± 6.9 |
| Day 3 | 86.2 ± 10 | 131.2 ± 17.2 | 102.7 ± 5.6 |
| Day 7 | 82.9 ± 16 | 187.9 ± 59.3 | 103.4 ± 13.2 |
| Day 11 | | | |
| p Value | NS | <.001 | <.001 |

Valine (155-330 μmol/L) | 195.3 ± 28.9 | 241.8 ± 33.6 | 182 ± 16.3 |
| Day 0 | 272.2 ± 24.4 | 445.8 ± 33.4 | 297.4 ± 29.3 |
| Day 3 | 283.4 ± 19.1 | 465.3 ± 40.8 | 275 ± 36.8 |
| Day 7 | 195.1 ± 34.5 | 416.8 ± 41.2 | 281 ± 45.3 |
| p Value | NS | <.0001 | <.04 |

Group A, B, C: p < .05

Plasma concentrations of arginine increased during the study period in group B (from 100+/-.14 to 174+/-.48 micro mol/L, NS), and reached statistical significance in group C (from 83+/-.8 to 112+/-.2 micro mol/L, p < .05).

Plasma concentrations of glutamine showed no significant difference during the study period (Table 7).
Table 7. Glutamine and arginine (mean +/- SEM)

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glutamine (535 ± 100 μmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>321.9 ± 33.3</td>
<td>358.8 ± 46.8</td>
<td>303.2 ± 27</td>
</tr>
<tr>
<td>Day 3</td>
<td>320.3 ± 27.5</td>
<td>373.5 ± 37.8</td>
<td>370 ± 41</td>
</tr>
<tr>
<td>Day 7</td>
<td>318.9 ± 21.1</td>
<td>414 ± 51.2</td>
<td>343.3 ± 29.9</td>
</tr>
<tr>
<td>Day 11</td>
<td>285 ± 54</td>
<td>374 ± 24.6</td>
<td>384.7 ± 39.7</td>
</tr>
<tr>
<td><strong>Arginine (535 ± 100 μmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>80.6 ± 9.8</td>
<td>100 ± 14.3</td>
<td>83.8 ± 9.5</td>
</tr>
<tr>
<td>Day 3</td>
<td>126 ± 19.8</td>
<td>157.5 ± 17.4</td>
<td>108.5 ± 7.7</td>
</tr>
<tr>
<td>Day 7</td>
<td>105.2 ± 9.2</td>
<td>154 ± 14.6</td>
<td>118.5 ± 9.2</td>
</tr>
<tr>
<td>Day 11</td>
<td>99.1 ± 17.7</td>
<td>174.5 ± 48.2</td>
<td>112.8 ± 12.5</td>
</tr>
<tr>
<td><strong>p Value</strong></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

The length of stay in the ICU, including for nonsurviving patients, showed no significant differences among the groups studied (18.5 days in group A, 14.4 days in group B, and 17.8 days in group C).

Nine (40.9%) patients in group A, two (8%) patients in group B, and five (22.7%) patients in group C died as a result of multiple organ failure before being discharged from the ICU (p < .03, group A vs. groups B and C). Although the criteria for dismissing patients from the ICU were stabilization and good progress, two patients (one patient in group A and one patient in group C) died after ICU discharge. The global hospital mortality for the patients in the study was ten patients in group A, two patients in group B, and six patients in group C.

DISCUSSION

In the septic patients studied, an increase in the short-life plasma proteins was observed in those patients treated with high loads of branch-chain amino acids, and a relationship between plasma concentrations of leucine, isoleucine, valine, and arginine and branch-chain amino acids loads as part of a nutritional support regimen was observed. The major finding of the study was the lower mortality rate observed in the patient groups with high branch-chain amino acid loads (>or=to 0.5 g/kg/day).

The goals of parenteral nutrition in septic patients have been to provide appropriate calories and amino acids to meet energy requirements, reducing the increased catabolism and stimulating endogenous protein synthesis [16]. Controversy still exists concerning the optimal level and quality of energy and protein supplementation in sepsis. The use of enriched branch-chain amino acid formulations in sepsis has several theoretical advantages. Experimentally, the branch-chain amino acids have been shown to decrease protein degradation and to stimulate protein synthesis in liver and muscle [17-20]. In addition, they may be oxidized peripherally to serve as a fuel source and may be substrates for nonprotein energy production [21-23]. The branch-chain amino acids represent a unique source of energy in that the oxidation of the first carbon fragment yields high-energy phosphate without the intervention of glucose. This finding is of particular importance when other energy-producing mechanisms that use glucose are less functional, as in sepsis [22,24-29].

No complications or side effects from high doses of branch-chain amino acids have been published. In our septic patients, serum alkaline phosphatase concentrations showed a significant increase over the study period in group B, and glutamic oxalacetic transaminase concentrations increased in group C (patients receiving branch-chain amino acids-enriched formulations). These changes have been observed by others [10] and disappeared on discontinuing parenteral nutrition.

The results using high-concentration branch-chain amino acids solutions in septic patients are disappointing if one accepts nitrogen balance as being the criterion of efficacy [12,30-41]. The disparity of results may depend on the patient's nutritional status, degrees of stress, amounts of branch-chain amino acids infused, and type of non-protein energy supplied. In our study, the negative nitrogen balance decreased significantly during the study period for all of the patient groups studied. However, no positive nitrogen balance was obtained after 11 days of parenteral nutrition, and no statistical differences between groups were found in nitrogen balance evolution. The lack of significant differences in nitrogen balance between the solutions used was possibly due to the effective utilization of lipids as a fuel source, causing the nitrogen balance in all groups to improve, as has been observed by others [16]. The use of a balanced substrate for nonprotein calorie support may play an important role in critically ill patients, where an insulin-resistant state in skeletal muscle leads to reduced glucose uptake and decreased use of glucose as a fuel source. With the unavailability of other fuels, the skeletal muscle can utilize amino acids for energy [40,42-44].

A failure to demonstrate a consistent improvement in nitrogen balance following infusion of solutions containing high concentrations of branch-chain amino acids does not necessarily mean that the branch-chain amino acids have no effect on protein turnover. The absence, in general, of an observed effect on 3-methylhistidine excretion implies that the branch-chain amino acids nitrogen retention effect is not from reduced proteolysis, but more likely reflects...
Differential effects on hepatic protein synthesis with the use of branch-chain amino acids in sepsis may reflect an improvement in host defense, may reduce the frequency rate of multiple system organ failure, and may possibly influence survival [49,46]. The ability of the branch-chain amino acids to alter whole-body protein turnover was investigated in laboratory animals and in humans by several investigators [9,19,23,34,38,39,45]. Our results showed an improvement in plasma concentrations of prealbumin and retinol-binding protein in septic patients in response to infusion of a 45% branch-chain amino acids formulation compared with an infusion of a standard amino acid solution. Although prealbumin and retinol-binding proteins are hepatic proteins whose synthesis decreases during inflammatory states when amino acids are shunted into acute-phase proteins, the use of these two short-life proteins as nutritional markers during short-term nutritional support has been established in previous clinical trials [47,48].

Branch-chain amino acids-rich parenteral nutrition has been shown to correct the plasma amino acid imbalance that exists in sepsis and may be used to predict the severity and outcome of sepsis [49-53]. As expected, the changes of plasma amino acid profiles in our patients indicated that septic patients who received the high branch-chain amino acid solutions showed significantly higher plasma concentrations of valine, leucine, and isoleucine. The increased concentrations of these amino acids in our study were correlated with the branch-chain amino acids load administered. Group B, which received a higher amount of branch-chain amino acids (0.67 g/kg/day), increased plasma values of leucine, isoleucine, and valine above the normal reference limits. This result may reflect that for our patients, the branch-chain amino acids load of 0.5 g/kg/day (the dose administered to group C) was better than 0.67 g/kg/day. Jimenez et al. [34,52] observed that in septic patients, plasma concentrations of leucine and valine reached high concentrations after 15 days when solutions with high branch-chain amino acids concentration (45%) were used, suggesting that the need for branch-chain amino acids diminishes when the hypercatabolic state disappears.

Plasma concentrations of arginine increased in groups B and C, which received higher branch-chain amino acid loads. In laboratory animals and in patients, an increase in the plasma concentration of arginine in sepsis has been observed [18,54]. In our study, the patients with increased plasma concentrations of arginine received a lower amount of arginine with the parenteral nutrition administered. Nachbauer et al. [55] found in laboratory experiments that plasma concentrations of both valine and isoleucine correlated strongly with those of arginine and ornithine, suggesting enhanced ureagenesis. Ruderman and Lund [56] were the first to observe that addition of valine, leucine, and isoleucine to the perfusion medium of rat hindquarters increased the release of alanine and glutamine. Houdijk et al. [57] and Wakabayashi [58] observed that glutamine diets significantly increased arterial concentrations of glutamine, citruline, and arginine. It may be that valine and isoleucine donate their amino nitrogen directly to pyruvate as traditionally conceptualized; the alanine thus formed subsequently is deaminated in the liver, and the amino nitrogen is excreted as urea. In laboratory experiments, septic animals treated with a branch-chain amino acids parenteral nutrition-enriched solution showed a significant improvement in the survival rate compared with animals fed ad libitum [20], or animals treated with a solution containing no amino acid [18]. No influence on the outcome of patients has been related with the different branch-chain amino acid loads administered. Whether these metabolic support tools will impact on mortality is a matter of conjecture. Nonetheless, the primary role for muscle branch-chain amino acids metabolism is to provide nitrogen for the formation of glutamine, which is then used by cells of the immune and repair systems. The improvement in plasma short-turnover proteins may be a reflection of a rebalancing of protein kinetics in favor of protein synthesis; the milieu effect following a normalization of the plasma amino acid pattern may be another possibility. Due to the relationship between arginine, immune function, and nitric oxide, the increased arginine plasma concentrations may also play an important role in the outcome of our patients [59-61]. Moreover, in both liver failure and severe sepsis, changes in the plasma concentrations of aromatic amino acids and branch-chain amino acids result in an increase in the aromatic/branch-chain amino acids concentration ratio [62]. If the change in this ratio is severe, it may result in encephalopathy, which is sometimes seen in severe sepsis and is identical to the change seen with hepatic encephalopathy. Septic patients with encephalopathy have increased mortality rates as compared with those patients without encephalopathy [63].

In terms of severity (sepsis etiology, APACHE II score, inotropic drug requirements), there were no differences between any of the patients in any of the groups. The major difference between the groups was the amount of branch-chain amino acids administered. Therefore, the marked increase in prealbumin and retinol-binding protein, and leucine, valine, isoleucine and arginine plasma concentrations, and decreasing mortality rate would appear to have been significantly affected by the branch-chain amino acids. The patient group treated with 0.5 g/kg/day of branch-chain amino acids (group C) showed similar beneficial effects as the group that received 0.67 g/kg/day of branch-chain amino acids (group B), but without the higher concentrations of plasma valine, leucine, and isoleucine obtained in group B.

The present study provides evidence that the branch-chain amino acids-enriched solutions, even with less nitrogen intake, may be beneficial for septic patients [64]. This result is possibly secondary to the additive effects of the higher plasma concentrations of the rapid turnover proteins and valine, leucine, isoleucine, the preservation of glutamine concentrations, and the improvement in the arginine plasma concentrations.

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