Original Article

The effects of intravenous, enteral and combined administration of glutamine on malnutrition in sepsis: a randomized clinical trial

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Our aim was to compare the effects of intravenous, enteral, and enteral plus intravenous supplemented glutamine on plasma transferrin, nitrogen balance, and creatinine/height index in septic patients with malnutrition. Blood and urine samples were collected for transferrin, urea and creatinine measurements. Samples, SOFA score and protein-calorie intake values were repeated on days 7 and 15. Patients (n:120) were randomly divided into 4 groups. Group I received 30 g/day IV glutamine, group II received 30 g/day enteral glutamine, group III received 15 g/day IV and 15 g/day enteral glutamine. Group IV received only enteral feeding as a control group. Transferrin levels decreased in group IV (p<0.01 0-7 days, p<0.01 7-15 days, p<0.01 0-15 days). Nitrogen balance levels were highest in group IV when compared with group I (p<0.05, p<0.001), group II (p<0.001), and group III (p<0.05, p<0.001) on days 7-15. Creatinine/height indexes increased in group I (p<0.001), group II (p<0.001), group III (p<0.001), and group IV (p<0.05) on day 15. In group III the creatinine/height index was higher than in groups I and II (p<0.05). In group IV, creatinine/height index was lower than in group I (p<0.01) and group II (p<0.001). Protein-calorie intake in group IV was higher than others on day 7 (p<0.05). SOFA scores of group IV were higher than the other groups on day 15 (p<0.05). This study demonstrated, that combined route of gln supplementation resulted in the most positive outcome to transferrin, creatine/height index and nitrogen balance (on days 7 and 15) during the catabolic phase of septic patients with malnutrition.

Key Words: malnutrition, glutamine, sepsis, transferrin, nitrogen balance

INTRODUCTION

During the early stages of sepsis, a splanchnic hypoperfusion is initiated and it further amplifies the impairment of the gut barrier function and thus facilitates the translocation of bacteria.[1] Enteral nutritional support plays an important role in preventing bacterial translocation and ensuring optimal recovery in septic patients with malnutrition.[2] Enteral nutrition appears to be clinically beneficial, because it encourages the rapid return of gut function and reduces the cytokine-generated stress response that occurs during sepsis. Sepsis is a catabolic process and during catabolic processes, skeletal muscles release large amounts of glutamine (gln) into the blood and gln uptake is markedly increased by the tissues which use gln. Consequently, gln deficiency may cause a weakened response against oxygen radicals, a decreased immune response, impaired wound healing, malnutrition, and intestinal hyper-permeability which lead to bacterial translocation.[1] Hence, the use of gln is advised during sepsis.[3] Gln has both enteral and intravenous use.

Reaching the targeted protein-calorie intake levels in septic patients with malnutrition may be problematic and it could take days to reach the target levels. In such conditions, the amount of gln absorbed from the intestinal lumen is not known. During these periods, use of intravenous gln could be an appropriate choice or in some septic patients enteral gln can be favored as intravenous administration can increase the risk of catheter infection. Options for supplementing gln can change according to the clinical status of the patients. There are experimental studies comparing the use of intravenous and enteral gln use.[1,4] There have been dissimilar results reported.

Our aim was to compare the effects of intravenous, enteral and enteral plus intravenous supplemented gln on plasma transferrin levels, nitrogen balance and creatinine/height index in septic patients with malnutrition.

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MATERIALS AND METHODS

Patients' population and study design

This study is a prospective, randomized, single-blind, clinical trial approved by the Istanbul University Cerrahpasa Medical Faculty Ethics Committee. Informed consent was obtained from every patient's family. All patients' age, gender, height, and weight values were recorded. We calculated the Acute Physiology and Chronic Health Evaluation II (APACHE II) scores from clinical data available after the first 24 hours of intensive care. We calculated the SOFA scores and protein-calorie intake of all groups on days 0, 7, and 15.

Patients who met sepsis criteria and received a diagnosis of malnutrition with a "Subjective Global Assessment Test"-SGA- (Table-1) without any contraindication for enteral feeding were included in the study.[5]

Exclusion criteria included patients who had a contraindication for or who could not tolerate enteral feeding, with disturbances of fluid balance and electrolyte levels, who had already been parenterally fed, patients with no diagnosis of malnutrition, patients with hemodynamic instability, with chronic liver or kidney failure, who were diabetic or morbidly obese, and patients with bleeding diathesis.

Patients included in the study were admitted to the intensive care unit from various wards of the hospital. The protein-calorie intake needs of septic patients who were diagnosed with accompanying severe malnutrition (after SGA assessment), as they were admitted to intensive care unit, were calculated by Harris-Benedict formula.[6] The protein needs of the patients additionally were not calculated. Nasogastric tubes were placed and standard enteral nutrition products were started in the first 24th hour. In patients with hypoalbuminemia, 20% Human albumin replacement was implemented. The albumin levels of the patients were targeted to be over 2.5 g/dL. Gln administration was started with a dose of 30 g/day for all patients except the ones in the control group. The protein-calorie intake target calculated for each patient (5,6 kJ/kg/day) was planned to be reached in 72 hours, gradually. Patients who were not able to reach the calculated target in this period were excluded from the study. Protein-calorie intake needs were fulfilled by using intravenous nutrition products.

The person who collected the data for the study did not know which group the patient belonged to (single blind). Randomization was achieved by pulling slips of paper labeled I, II, III and IV from a bag (30 pieces per group).

Data collection

Blood and urine samples were collected for transferrin, urea and creatinine measurements before the randomization of the patients, after which 120 patients diagnosed with both malnutrition and sepsis were randomized into four groups (n:30) by pulling numbers from the bag.

Group I received 30 g/day IV gln (Dipepdiven, Fresenius-Kabi, Austria), Group II received 30 g/day enteral gln (Glutamine Resource, Nestlé, Swiss), Group III received 15 g/day IV and 15 g/day enteral gln (a total of 30 g/day) in addition to enteral feeding. Group IV received enteral feeding with no gln as a control group.

The measurements were repeated on days 7 and 15 of the study. Starting at the baseline and continuing on days 7 and 15, daily enteral intake was recorded in order to obtain transferrin levels, nitrogen balance and creatinine/height index.

Measurements were obtained on days 0, 7, and 15. Three consecutive 24-hour urine samples were collected from subjects, each from 7:00 a.m. until 7:00 a.m. of the day after.

Assay and calculations

Urinary concentrations of nitrogen, corrected for creatinine, were determined by the chemiluminescence method in the Cerrahpasa Medical Faculty Laboratory. Estimated nitrogen balance was calculated as the difference between total nitrogen intake and total nitrogen output in the urine. Nitrogen intake was calculated from the nitrogen provided in the actual measured intake of feeding tube feeds for each patient. The following formulas were used in calculating the nitrogen balance and creatinine/height index of the patients: [7,8]

- Nitrogen balance = 24 hour protein uptake/6.25-(24 hour nitrogen excretion + 4 g) Creatinine/height index %=(24 hour urine Creatinine)/24 hour ideal urine Creatinine × 100

The mean creatinine indexes expected from healthy young males and females were used to calculate the creatinine/height index.

A result of an index between 60-80% shows a medium protein consumption problem, and an index under 60% shows a profound protein consumption problem.[8]

The "Radial Immunodiffusion Technique" was used to measure serum plasma transferrin levels. The normal range is 150-200 mg/dL but a value under 100 mg/dL is a sign for grave consumption in critically ill patients.

Statistical analysis

Data were expressed as the mean±SD. Sample sizes of 30, 30, 30 and 30 are obtained from the 4 groups whose means are to be compared. The total sample of 120 subjects achieves 95% power to detect a difference of at least

Table 1. Patients' baseline demographic data

	Group I (n=30)	Group II (n=30)	Group III (n=30)	Group IV (n=30)
Gender (F/M)	13/17	16/14	14/16	15/15
Age (year)	57.9±18.9	55.6±17.0	57.5±17.7	56.5±13.6
Weight (kg)	69.5±11.2	69.3±12.0	70.3±12.3	69.0±11.9
Height (cm)	164 ±16.5	168±17.6	162±8.2	166±9.3
APACHE II	18.2±7.9	19.4±4.4	19.6±4.8	17.5±3.9
SGA	2.5±0.5	2.3±0.8	2.4±0.6	2.3±0.7
MV duration	13.0±12.2	13.0±6.5	12.9±5.3	14.3±5.4

Table 2. Comparison of transferrin levels between groups (mg/dL)

	Group I (n=30)	Group II (n=30)	Group III (n=30)	Group IV (n=30)
Transferrin 0 day	80.7±11.6	75.7±9.6	73.3±10.6	83.6±12.5
Transferrin 7 day	90.5±15.1^{a}	98.9±11.8$^{aa\beta}$	93.4±10.5$^{a\acute{a}}$	70.5±17.6$^{aa\S\#\dagger\dagger}$
Transferrin 15 day	128±24.5^{***bbb}	119±11.1^{*bbb}	138±20.9$^{**bbb\acute{a}\acute{a}}$	61.7±10.4$^{**bb\S\S\S\#\#\dagger\dagger\dagger}$

$^{a}p<0.05$, $^{aa}p<0.01$ comparison within group at 0-7 days, $*p<0.05$, $**p<0.01$, $***p<0.001$ comparison within group at 7-15 days
$^{bb}p<0.01$, $^{bbb}p<0.001$ comparison within group at 0-15 days, $^{\beta}p<0.05$ comparison between groups 1 and 2, $^{\acute{a}}p<0.05$ comparison between groups 1 and 3, $^{\S}p<0.05$, $^{\S\S\S}p<0.001$ comparison between groups 1 and 4, $^{\#}p<0.01$, $^{\#\#}p<0.001$ comparison between groups 2 and 4, $^{\dagger\dagger}p<0.01$, $^{\dagger\dagger\dagger}p<0.001$ comparison between groups 3 and 4

Table 3. Comparison of nitrogen balance between groups

	Group I (n=30)	Group II (n=30)	Group III (n=30)	Group IV (n=30)
N 0 day	-7.5±4.7	-11.1±3.4	-14.3±5.9	-10.8±4.0
N 7 days	-12.3±5.8^{a}	-11.8±3.5$^{a\beta}$	-11.0±2.6$^{\acute{a}\acute{a}\acute{a}}$	-11.0±4.5$^{a\S\#\dagger}$
N 15 days	-3.0±0.3^{***bbb}	-3.3±2.4^{***bbb}	-1.2±0.6$^{***bbb\acute{a}\beta}$	-8.0±3.7$^{**bb\S\S\S\#\dagger\dagger\dagger}$

$^{a}p<0.05$ comparison within group at 0-7 days, $**p<0.01$, $***p<0.001$ comparison within group at 7-15 days, $^{bb}p<0.01$, $^{bbb}p<0.001$ comparison within group at 0-15 days, $^{\beta}p<0.05$ comparison between groups 1 and 2, $^{\acute{a}}p<0.05$, $^{\acute{a}\acute{a}\acute{a}}p<0.001$ comparison between groups 1 and 3 $^{\S}p<0.05$, $^{\S\S\S}p<0.001$ comparison between groups 1 and 4, $^{\#}p<0.01$ comparison between groups 2 and 4, $^{\dagger}p<0.05$, $^{\dagger\dagger\dagger}p<0.001$ comparison between groups 3 and 4

10.00 using the Tukey-Kramer (Pairwise) multiple comparison test at a 0.05 significance level. The common standard deviation within a group is assumed to be 5.00.

When comparing the four groups, One way ANOVA was used in the parameters that showed normal distribution, and Bonferroni was used as post-hoc test. When comparing numerical parameters that showed non-normal distribution between groups, Mann Whitney U test was used. In repetitive parameters that showed normal distribution Variance Analysis and in repetitive parameters that showed non-normal distribution Friedman Variance Analysis was used. In the comparison of categorical variables crosstab statistics were used. Differences between groups were considered significant at $p<0.05$.

RESULTS

There were no differences between groups in terms of sex, age, weight, height, and APACHE II scores, SGA and the duration of mechanical ventilation (Table 1).

Plasma transferrin

Plasma transferrin levels increased in group I ($p<0.05$ from days 0-7, $p<0.001$ from days 7-15 as well as from days 0-15), in group II ($p<0.01$ from days 0-7, $p<0.05$ from days 7-15, $p<0.001$ from days 0-15), and in group III ($p<0.05$ from days 0-7, $p<0.01$ from days 7-15, $p<0.001$ from days 0-15) (Table 1). Plasma transferrin levels decreased in group IV ($p<0.01$ from days 0-7 and 7-15, $p<0.01$ from days 0-15) (Table 2).

Plasma transferrin levels in group I were lower than in groups II and III ($p<0.05$) on day 7. Plasma transferrin levels in group I were higher than in group IV ($p<0.001$) and lower than group III ($p<0.01$) on day 15. Plasma transferrin levels in group II were lower than in group III ($p<0.01$) on day 15. Plasma transferrin levels in group II were higher than in group IV on day 7 ($p<0.01$) and on day 15 ($p<0.001$). Plasma transferrin levels in group III were higher than in that found in group IV ($p<0.01$) on days 7 and 15 ($p<0.001$) (Table 2).

Nitrogen balance

Nitrogen balance levels increased negatively in groups I, II, and IV ($p<0.05$ from days 0-7). However, in group III, the nitrogen balance did not change from days 0-7 (Table 2). Nitrogen balance levels decreased in groups I, II and III ($p<0.001$ from days 7-15 as well as from days 0-15). Nitrogen balance levels decreased with a lower degree of significance in group IV ($p<0.05$ from days 0-7, $p<0.01$ from days 7-15 as well as from days 0-15) (Table 3).

Nitrogen balance levels in group I were higher than in group II ($p<0.05$), group III ($p<0.001$) and group IV ($p<0.05$) on day 7; nitrogen balance levels in group I were lower than in group III ($p<0.05$) on day 15; and in group I nitrogen balance levels were lower than in group IV ($p<0.001$) on day 15. Nitrogen balance levels in group II were higher than in group III ($p<0.05$) and group IV ($p<0.01$) on day 7; nitrogen balance levels in group II were higher than in group III ($p<0.01$) on day 15; and in group II nitrogen balance levels were lower than group IV ($p<0.01$) on day 15. Nitrogen balance levels in group III were lower than in group IV on day 15 ($p<0.001$) (Table 3).

Creatinine/Height Index (C/H)

There were no differences in C/H indexes in days 0-7 within groups III and IV. In groups I and II, C/H indexes decreased ($p<0.05$ from days 0-7). C/H indexes increased in group I ($p<0.001$), group II ($p<0.001$), group III ($p<0.001$) and group IV ($p<0.05$) on days 7-15 and on days 0-15 (Table 4).

The C/H index in group I was lower than in group III ($p<0.01$) and group IV ($p<0.001$) on day 7. The C/H index in group I was lower than that found in group III ($p<0.05$) and higher in group II than in group IV ($p<0.01$) on day 15. The C/H index in group II was lower than in group III ($p<0.01$) and group IV ($p<0.001$) on day 7. The C/H index in group II was lower than in group III ($p<0.05$) and higher than group IV ($p<0.01$) on day 15. The C/H index in group III was higher than in group IV ($p<0.01$) (Table 4).

Protein-calorie intake

Protein-calorie intakes increased within groups I, II, III and IV ($p<0.05$ for group I, II and III, $p<0.01$ for group IV from days 0-7). Protein-calorie intakes decreased within groups I, II, III ($p<0.05$ from days 7-15). Protein-calorie intakes decreased within groups I, II, III *($p<0.05$* for group I, III, $p<0.01$ for group III from days 0-15). Protein-calorie intake increased within group IV ($p<0.01$ from days 0-15) (Table 5).

Protein-calorie intake in group IV was higher than group I, II and III on day 7 ($p<0.05$). The protein-calorie intake in group IV was higher than group I *($p<0.05$)*, II ($p<0.01$), and III ($p<0.01$*)* on day15 (Table 5).

SOFA scores

SOFA scores increased within groups I, II, III and IV ($p<0.05$ from days 0-7). SOFA scores decreased within groups III ($p<0.05$ from days 7-15). SOFA scores increased within groups IV ($p<0.05$ from days 7-15) (Table 5).

There were no differences in SOFA scores between groups on day 7. SOFA scores in group IV was higher than group I, II and III on day 15 ($p<0.05$) (Table5).

DISCUSSION

In most septic patients, a negative nitrogen balance is often associated with poor clinical outcome.[9] Following severe metabolic stress such as sepsis, the synthesis and release of gln is insufficient to meet demands. Gln is a conditionally essential amino acid in the catabolic state, and has been shown to improve negative nitrogen balance.[1-3,10] Gln plays a significant role in different biochemical processes such as protein and nucleic acid synthesis. Gln is also an important nitrogen donator for many anabolic processes.[11, 12] It is known to serve as a primary fuel for rapidly dividing cells, such as in the gut and immune system, and is used as a source of nitrogen to refill the citric acid cycle.[13]

Today, early feeding of critical patients and if possible preferring of the enteral route is suggested.[2] In critical patients diagnosed with sepsis, intravenous route should be used as additional support if targeted protein-calorie levels can not be reached by enteral nutrition alone.

There are no clinical studies that evaluate the effects of enteral and intravenous gln on patient nutrition in sepsis. Synchronous enteral and intravenous use can be more efficient.

Our aim was to compare the effects of intravenous, enteral and enteral plus intravenous supplemented gln on plasma transferrin levels, nitrogen balance and creatinine/height index in septic patients with malnutrition.

Sahin *et al* [14] administered 0.3 g/kg/day IV gln to 40 patients diagnosed with acute pancreatitis and found that the transferrin levels in the gln IV group increased by 11.7%. The transferrin levels in the group that did not receive gln suffered a decrease of 12.1%, and hence they concluded that in patients with acute pancreatitis who are receiving parenteral feeding, IV gln has a beneficial effect on transferrin level.

De Urbina *et al* [15] fed 36 male Wistar rats parenterally. Control rats received 20 g/L less protein when compared with the study group. On day 7 of the study, in the group that did not receive gln, the transferrin levels were found to have decreased and nitrogen balance to have shifted into the negative, whereas in the group that received ALA-GLN showed no such differences and had a positive nitrogen balance.

In the Wischmeyer study, the control group was given equal amount (isonitrogenous) of protein/kg/day compared to the study group. However, the protein supplemented in the control group was by enteral route.[16] They found that the transferrin levels increased in 13 patients with burn degrees between 25-90% who were given IV gln when compared with the control group on day 14.

Various biochemical parameters are used in the evaluation of nutrition. Although albumin is one of those parameters, because of its longer half-life (18 days), it is not used in the evaluation of acute changes. Transferrin is a

Table 4. Comparison of C/H indexes between groups

	Group I (n=30)	Group II (n=30)	Group III (n=30)	Group IV (n=30)
C/H 0 day (%)	61.9±3.2	50.2±3.4	53.5±6.8	58.2±7.9
C/H 7 days (%)	46.6±5.9^{a}	45.6±5.5^{a}	54.4±4.5$^{\acute{a}\acute{a}}$	57.4±5.7$^{\S\S\S\neq\neq}$
C/H 14 days (%)	81.9±4.4^{***bbb}	77.5±6.5^{***bbb}	84.4±4.2$^{***bbb\acute{a}}$	65.3±4.0$^{b*\S\S\neq\neq\dagger\dagger}$

$^{a}p<0.05$ comparison within group at 0-7 days, $*p<0.05$, $***p<0.001$ comparison within group at 7-15 days, $^{b}p<0.05$, $^{bbb}p<0.001$ comparison within group at 0-15 days, $^{\S\S}p<0.01$ §§§, $^{\acute{a}}p<0.05$ comparison between groups 1 and 3, $^{\S\S}p<0.01$ $^{\S\S\S}p<0.001$ comparison between groups 1 and 4, $^{\neq\neq}p<0.01$, $^{\neq\neq\neq}p<0.001$ comparison between groups 2 and 4, $^{\dagger\dagger}p<0.01$ comparison between groups 3 and 4

Table 5. Comparison of protein-calorie intake/day and SOFA scores between groups

	Group I (n=30)	Group II (n=30)	Group III (n=30)	Group IV (n=30)
Protein-Cal/day 0	1579±151	1590±163	1556±198	1549±152
Protein-Cal/day 7	1752±196^{a}	1740±174^{a}	1738±175^{a}	1807±151$^{aa\S\neq\dagger}$
Protein-Cal/day 15	1539±135*	1495±99.9^{*bb}	1488±120^{*b}	1708±146$^{*bb\S\neq\dagger\dagger}$
SOFA day 0	8.4±1.7	8.1±1.3	8.2±1.8	8.4±2.6
SOFA day 7	9.5±2.2^{a}	9.3±2.9^{a}	9.5±2.3^{a}	9.3±2.1^{a}
SOFA day 15	9.1±1.9^{b}	9.1±2.5^{b}	8.9±2.0*	10.0±2.3$^{*bb\S\neq\dagger}$

$^{a}p<0.05$, $^{aa}p<0.01$ comparison within group at 0-7 days, $*p<0.05$ comparison within group at 7-15 days, $^{b}p<0.05$, $^{bb}p<0.01$ comparison within group at 0-15 days, $^{\S}p<0.05$, $^{\S\S}p<0.01$ comparison between groups 1 and 4, $^{\neq}p<0.05$, $^{\neq\neq}p<0.01$ comparison between groups 2 and 4, $^{\dagger}p<0.05$, $^{\dagger\dagger}p<0.01$ comparison between groups 3 and 4

protein synthesized in the liver, which enables iron transportation and reflects acute changes better than albumin because of its shorter half-life (8 days).[17]

The patients in our study all had serum transferrin levels under 100 mg/dL, a sign of critical illness. In all patients in three groups who received gln, the transferrin levels started to increase by day 7 of the study. On day 15, all transferrin levels were above 100 mg/dL. In group III, which received both parenteral and enteral gln, transferrin levels were close to normal values. In group IV that did not receive gln but had enteral feeding directed only by formula calculation, transferrin levels started to decrease by day 7, and on day 15 they were below starting levels. It is a fact that the addition of either enteral or parenteral gln to the diet increases transferrin synthesis, and our study showed that parenteral and enteral gln given together was more effective than gln given by only one (enteral or iv) route.

Peng *et al* [18] gave 0.5 g/kg/day oral gln granules for 14 days to 25 of 48 severely burned patients who received standard enteral feeding. At the end of day 14, the transferrin levels of the group who received gln were found higher and urine nitrogen excretion decreased.

Forty-eight hours before the anesthesia induction, Dock–Nascimento *et al* [19] gave 40 g of gln with 50 g of maltodextrin to 24 of 48 patients who were scheduled to undergo laparoscopic cholecystectomy. They gave 10 g gln and 25 g maltodextrin to the same group 2 hours before anesthesia induction. The control group was given only maltodextrin and water in the same study protocol. When pre- and postoperative nitrogen balances were compared, nitrogen balances in the gln group were found to be less negative.

Luo *et al* [20] divided 44 enterally fed patients into 3 groups. The first group (n=15) did not receive any gln support; the second group (n=15) received 0.5 g/kg/day enteral gln and the third group (n=14) received 0.5 g/kg/day IV gln. The study lasted for 9 days and nitrogen balance was evaluated on days 6 and 9. They found that nitrogen balance was negative in the third group who did not receive any gln support.

Lu *et al* [21] added gln-enriched iv isocaloric total parenteral nutrition therapy to 25 of 50 patients with gastrointestinal cancers. On day 7, nitrogen balance values were better in the group that received gln when compared to the control group.

Fuentes-Orozco *et al* [22] administered gln supplemented parenteral nutrition therapy in 22 of 44 patients with acute pancreatitis and showed that the nitrogen balances improved on days 5 and 10 in the group with the gln support.

Urine nitrogen excretion is used to assess the sufficiency of protein support in the nutrition therapy. Nitrogen balance is the metabolic equilibrium between the protein the patient gets and the physiological and pathological losses of protein.[7] We used the Harris-Benedict formula to calculate protein-calorie intake needs of the groups on days 0, 7 and 15. We found that on day 7, the protein-calorie intake needs increased whereas it decreased below the initial levels in day 15, except in the group that did not receive gln support. This change is concurrent with the changes of nitrogen balance. Judging these two parameters, we can conclude that the addition of gln has a positive effect on the nutrition therapy of the patients. Synchronous use of enteral and intravenous gln has a statistically significant positive effect on the protein-calorie intake needs and nitrogen balance. Although intravenous use of gln yields better results than enteral use, this difference is not statistically significant. Prior studies support this finding.

The creatinine/height index is a follow up parameter in nutrition therapy. We were only able to express our own creatinine/height index data for we were not able to locate any similar article with which we could compare our data. The creatinine/height index is used to evaluate the creatinine excreted from the body and is directly proportional with the skeletal muscle mass.[8]

In our study, the creatinine/height indexes in all of the groups were between 50% and 60%. These values increased on day 15. The fastest and most evident change was in group III (which received both enteral and parenteral gln) on day 15. Only the group with combined IV and enteral gln supplementation was able to achieve the initial creatinine/height index value as early as 1 week after ICU admission, but this was not statistically significant. For reasons unknown, it is speculated that the combined route of gln administration facilitates a more efficient utilization of exogenous substrate toward a more clinical significant protein synthesis not seen in either intravenous or enteral routes alone.

In our study, the SOFA score, an evaluator of organ dysfunction, was highest on day 15 in group IV that did not receive gln support. However the duration of the mechanical ventilation support did not differ statistically between groups although it was arithmetically different.

Our study demonstrated that gln supplementation via either route exert a beneficial effect on the maintenance of a positive nitrogen balance during the catabolic phase in septic patients with malnutrition.

The uniqueness of this study comes from the fact that combined route of gln supplementation resulted in the most rapid and positive outcome on transferrin and nitrogen balances at days 7 and 15, on a specific group of patients who were able to tolerate early enteral feeding during sepsis. We favor the supplementation of 30g/day gln in the form of combined intravenous and enteral route with a 50:50 ratio.

Limitations for this study include the lack of measurement of plasma amino acids which in humans is very expensive, impractical and nearly impossible in studies with higher participant numbers. Therefore, studies are needed to evaluate the histopathologic effects of administration of gln from two different routes on the absorption in septic and malnutrition. However, studies of this kind can only be experimental.

Conclusion

This study demonstrated that, a combined route of gln supplementation resulted in the most positive outcome in terms of transferrin, C/H index and nitrogen balance (at day 7 and 15) during the catabolic phase, in septic patients with malnutrition.

AUTHOR DISCLOSURES

Authors declare no conflicts of interest or funding disclosure.

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Original Article

The effects of intravenous, enteral and combined administration of glutamine on malnutrition in sepsis: a randomized clinical trial

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比較由靜脈輸入或腸道攝取或合併使用的方式補充麩醯胺酸對營養不良之敗血症病患的效果：隨機臨床試驗

本研究目的為比較以不同途徑補充麩醯胺酸，分別為靜脈輸入、腸道攝取、及靜脈輸入合併腸道攝取三種方式，對於營養不良之敗血症病患，其血漿運鐵蛋白、氮平衡與肌酸酐/身高指數之效果。收集血液和尿液樣本，用於測量運鐵蛋白、尿素和肌酸酐。在試驗第 7 及 15 天重複收集生化樣本、執行器官衰竭評分(SOFA score)與記錄蛋白質熱量攝取量。將 120 位病患隨機分配到四組。第一組每日以靜脈營養方式補充 30 g 麩醯胺酸；第二組每日由腸道攝取 30 g 麩醯胺酸；第三組每日以靜脈輸入 15 g 麩醯胺酸，再加上腸道攝取 15 g 麩醯胺酸；第四組為控制組，以腸道營養進食。運鐵蛋白數量在第四組顯著減少(0-7 天 $p<0.01$；7-15 天 $p<0.01$；0-15 天 $p<0.01$)。氮平衡在第 7 及 15 天，與第一組($p<0.05$, $p<0.001$)、第二組($p<0.001$)、第三組($p<0.05$, $p<0.001$)比較，第四組為最高。肌酸酐/身高指數在第 15 天各組均有顯著提升。第三組肌酸酐/身高指數比第一組及第二組高；第四組則比第一組及第二組低。蛋白質熱量攝取量在第 7 天，第四組較其他組別高($p<0.05$)。器官衰竭分數在第 15 天，第四組較其他組高($p<0.05$)。本研究顯示，結合腸道與靜脈營養的途徑補充麩醯胺酸，對於營養不良之敗血症病患，其運鐵蛋白、肌酸酐/身高指數與氮平衡有最正面的效果(在第 7 與 15 天)。

關鍵字：營養不良、麩醯胺酸、敗血症、運鐵蛋白、氮平衡