Effects of glutamine in critical illness

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ABSTRACT

Objectives: Under normal physiological conditions, glutamine is synthesized in large amounts by the human body and is considered nonessential. It has been hypothesized that glutamine may become a conditionally essential amino acid in patients with catabolic disease. The objective of this study is to investigate the prognostic effect of glutamine.

Methods: For this study, we selected 48 patients from the intensive care unit. Group I consisted of 33 patients whose treatment included glutamine. We placed the remaining 15 patients in group II, and they did not receive glutamine in their treatment. We retrospectively investigated treatment time, leucocyte levels and outcome. We carried out the study between January 2002 and January 2003 in Konya Governmental Hospital, Turkey.

Results: The average duration of hospital stay in the glutamine group was 8 ± 1.2 days, 58% of them leaving hospital with surrogate. However, in the group whose treatment did not include glutamine, 42% of them left the hospital surrogate, their average hospital stay being 12 ± 3 days. In the group receiving glutamine in the treatment, there was a prominent decrease in leukocyte levels compared to the other group, and hospitalization times were shorter but there was no statistically significant difference in mortality or survival rates.

Conclusions: Glutamine may decrease the catabolism. It may also have a positive effect on treatment time and the consequences of therapy in critically ill patients.

Critically ill patients are often in a prolonged catabolic condition and prone to malnutrition. Even vigorous nutritional support cannot prevent loss of lean body tissue and may be harmful by increasing the risk of metabolic disorders.[1] Catabolism is also seen to be prone to increase in all patients who cannot be fed orally. In critically ill patients, gastrointestinal failure and intolerance to gastrointestinal tube are very common. Patients often require parenteral nutrition support. Malnutrition is common in patients admitted to the intensive care unit (ICU) and can be exacerbated by a prolonged stay.[2]

Following critical illness, sepsis remains a major cause of morbidity and mortality. Previously, the pathogenesis of sepsis and the systemic inflammatory syndrome (SIRS) have been explained in terms of persistent, uncontrolled inflammation. Then counter-regulatory mechanisms were removed from consideration, and it was called compensatory anti-inflammatory response syndrome (CARS). The relative magnitude of these responses determines the patient's response to a critical illness. Additionally, critically ill patients may be predisposed to infectious complications due to impaired function of the immune system resulting from CARS dominance, an impairment which may occur very early on in the illness.

It has now been established that specific nutritional supplementation can influence the

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immune response, a concept known as immune-nutrition and much of this work has centered on the provision of the amino acid, glutamine.[3] Critically ill patients may be at increased risk of infection due to impaired immune function early during their illness. Multiple factors were associated with new infection including mechanic ventilation, diagnosis of trauma, the use of invasive devices, and the duration of ICU stay. Glutamine is the most abundant of the free amino acids in the human body and its concentration in plasma is the highest of all free amino acids (0.5 - 0.8 mmol out of 2.0 - 2.5 mmol). In muscle, the concentration is high, approximately 20 mmol of a total of 30 mmol. Other tissues, such as intestinal mucosa, liver and white blood cells, also have high glutamine concentrations, although not as high as muscle.[4]

The amino acid glutamine plays a central role in nitrogen transport within the body, is a fuel for rapidly dividing cells, such as those found in the intestine and immune system, and has many other essential metabolic functions.[5] Glutamine provides a source of energy through its partial oxidation in a process known as glutaminolysis, and provides carbon and nitrogen to precursors of nucleotide synthesis; it is also a precursor of intracellular glutathione, hepatic glucose and urinary ammonia.[6] Under normal physiological conditions, glutamine is synthesized in large amounts by the human body and is, therefore, considered to be nonessential. It has been hypothesized that glutamine may become a conditionally essential amino acid in patients with catabolic disease.[7] Several studies have shown that glutamine levels drop following extreme physical exercise, after major surgery, and during critical illness, although during critical illness, there is an increase in uptake of glutamine by the kidneys, immune cells and intestinal mucosa. Lower levels of glutamine have been associated with immune dysfunction and higher mortality in critically ill patients.[5]

Human studies suggest that glutamine supplementation maintains gastrointestinal structure,[8] and is associated with decreased intestinal permeability compared to standard total parenteral nutrition.[9] Although the increased permeability correlates with the development of organ dysfunction in critically ill patients, it may not correspond with an increase in bacterial translocation.[10] In humans, glutamine supplemented formulae have resulted in greater preservation of skeletal muscle, improved nitrogen balance,[11] enhanced immune cell function,[12] and no elevation in proinflammable cytokine production.[13] As glutamine is a precursor to glutathione, it has been demonstrated that glutamine supplementation results in higher levels of glutathione and anti-oxidative capacity.[14] Nevertheless, these findings in seriously ill patients have not yet been

clearly established. In addition, some studies have shown that supplementing internal and parenteral feeds with glutamine improves T-cell function and enhances the bactericidal function of neutrophils. This decreases the frequency of pneumonia, sepsis and bacteria in ICU trauma patients.[15]

In this study of critically ill patients who were taken to our ICU, and who could not be fed orally, we retrospectively compared the hospitalization time, leukocyte levels and mortality rates of those who received glutamine supplementation therapy and those who did not.

Methods. Hospitalization time, 3 days of leukocyte levels and mortality rates were examined retrospectively in critically ill patients, who applied to the emergency service of Konya State Hospital, were taken to the ICU and who could not be fed orally. A total of 48 patients (28 males and 20 females) were included in the study. Their average age was 54±22. The patients with similar diagnosis were divided into 2 groups: group I consisting of patients (n=33) who received glutamine supplementation therapy, and group II, those who did not (n=15). Hospitalization time, leukocyte levels on days 1, 2 and 3 after admission and mortality rates of patients in both groups were examined with appropriate statistical methods using the SPSS 11.0 program. Data were first applied to the normality test. Alteration in levels of group I and group II through time were analyzed with repeated measures of analysis of variants. Mortality times in both groups were examined with the life analysis method of Kaplan Maier, and chi-square analysis was used to compare mortality rates. Hospitalization times were examined using the Mann-Whitney-U test, because they did not show a normal allocation.

Results. The group receiving treatment including glutamine (group I), and the group which did not receive glutamine (group II) consisted of patients with similar diagnoses. Nine of the patients in group I were diagnosed with septic shock and septicemia, while 8 of them had multi-trauma, 7 cerebral edema and 9 were diagnosed with coma. Six of the patients in group II were diagnosed with septic shock and septicemia, 5 with multi-trauma, 2 with cerebral edema and 2 were diagnosed with coma. The leukocyte levels of the patients in 1st, 2nd and 3rd days were 19373±5150, 17273±5451, 15173±6593 (mean±SD) for group I and 2116±73267, 20760±4219, 1865±33300 (mean±SD) for group II. When the leukocyte levels of the 2 groups were analyzed periodically on the 1st, 2nd and 3rd days, group I levels were found to show a significant decrease compared to group II levels (*p*=0.013).

When time between admission to hospital and death was examined, mean mortality days was established as 12.64 in group I and 14.05 in group II, but no statistically significant distinction was established between the 2 groups (p=0.83).

Mortality rate was established as 30.3% in group I and 53.3% in group II. But, no significant distinction was established between the mortality rates of the 2 groups (p=0.228). When hospitalization times of patients in both groups were investigated, mean hospitalization time was established as 7.3±3.8 in group I and 10.8±3.3 in group II. The distinction between the 2 groups was statistically quite significant (p=0.001).

Group I patients, who received glutamine supplementation therapy, showed a definite decrease in leukocyte levels compared to the other group, and hospitalization times were shorter, but the differences in mortality rates and survival were not statistically significant.

Discussion. Several clinical trials have evaluated the effect of glutamine supplementation in seriously ill patients. Clinical effects of glutamine and results have been mostly examined in these studies. In our study, similar results have been examined, including the effect of glutamine supplementation therapy on hospitalization times and mortality rates.

Unlike other studies, we investigated the influence on the leukocyte-time and the leukocyte count on days 1, 2 and 3 of 2 case groups, compared with leukocyte values of similar case groups. Compared to the other group, a significant decrease was established in the number of leukocytes in patients taking glutamine. Glutamine facilitates the body's immune response. When the diagnoses of the cases in our study were examined, we see the increase of leukocyte levels as a response of the body to all these illnesses. Decrease in leukocyte levels may also be a precursor of a good prognosis. Taking all these factors into account, one might think that glutamine has a positive effect. Likewise, the hospitalization time was seen to shorten in patients on glutamine therapy. Thus again, glutamine may be thought to have a positive effect in this case. It has been established in our study that although glutamine supplementation therapy has the effect of decreasing mortality, the decrease is not statistically significant, a finding in accordance with the results of the other studies in the literature.

Glutamine levels play a vital role in the immune system. A striking feature of the immune system is that despite the difference in function and cell biology, all cells are dependent on glutamine in a similar manner. All cells show high rates of glutamine consumption in culture; most of the glutamine is not fully oxidized but converted to glutamate, lactate and aspartate. The high rates of glutamine utilization exceed the need for energy and nucleotide precursors, and it has been hypothesized that the high rate of glutaminolysis provides for precision in regulating changes in the rate of synthesis of nucleotides. In addition, the optimal phagocyte and secretor activity of immune cells may be dependent on adequate glutamine.[16]

Glutamine has a range of metabolic functions in addition to marked stimulatory and modulator actions in the immune system. Animal and human studies have shown that, after surgical stress, trauma or severe illness, plasma glutamine concentration declines. Exogenous glutamine is, therefore, given from the position of a state of deficiency, and supplementation of feeds may reflect the replacement of a nutrient that has become essential during that catabolic state. Stable isotope studies in the critically ill have confirmed a systemic demand for glutamine, with large fluxes of glutamine from skeletal muscle. Despite increased glutamine synthesis, normal intramuscular glutamine levels could not be maintained. Immune system activation with its requirement for increased glutamine use, nucleotide synthesis, protein synthesis and division, and energy supply is one hypothesis to explain the observed fluxes from skeletal muscle. Animal and ex vivo studies on lymphocytes have found a striking dose–response relationship at physiological plasma glutamine concentrations that is critical for T-lymphocyte function. The immune efficacy of glutamine therapy has been related to the dose and may exert most of its action through restoring optimal immune function and reducing the severity of invasive infections.[17]

Glutamine may have a direct effect on the immune system. Glutamine-enriched diets in mice increased the proportion of CD4+ lymphocytes in the spleen, increased the proportion bearing of the interleukin-2 receptor, and increased interleukin-2 production. Similarly, in stimulated macrophages, the production of tumor necrosis factor- , interleukin-1ß, and interleukin-6 were enhanced. These features, indicative of enhanced Th1-lymphocyte response, should lead to improved cell-mediated immunity toward bacteria, fungi and viruses. Glutamine parenteral nutrition improved survival in rats with abdominal sepsis.[18] Glutamine protected against apoptosis in immune and endothelial cell lines, which is induced by sepsis, and enhanced the protective expression of heat-shock proteins and survival from end toxin shock in rodents.[17] In mice, parenteral glutamine improved the primary immune defenses against infections of all mucosal surfaces, including the respiratory system, probably by optimizing lymphocyte function in the gut-associated lymphoid tissue and the production of secretor immunoglobulin A.[19] In a rat model, prolonged total parenteral nutrition (TPN) with glutamine not only

maintained mucosal morphology and reduced bacterial translocation but also completely abolished catheter infections.[20] The ICU trauma patients given enteral glutamine showed a potentially beneficial change in the CD4:CD8 T-cell ratio.[21] Delivery of 30 g/d of glutamine jejunely in multiple-trauma patients significantly reduced pneumonia, bacterial infection, and severe sepsis. Glutamine TPN in allergenic bone-marrow-transplant patients resulted in fewer clinical infections and a larger number of total lymphocytes and CD4 lymphocytes.[22] In all these studies, we see the positive effects of glutamine on the immune system. In our study, a faster and more expressive decrease in the number of leukocytes has occurred that can be thought as a sign of reducing infection. The amelioration process is faster in glutamine-treated patients.

Although there is a wealth of material on this subject in the literature, there has been no real consensus in the replacement of glutamine which is still a matter of discussion. Griffiths et al[22] randomized 84 critically ill patients with gastrointestinal failure to glutamine-containing parenteral nutrition. Study patients received a median of 6 days (inter-quartile range 3.2-11 days) of glutamine–supplemented parenteral nutrition. Overall, there was no difference in rate of infectious complications or ICU admission or hospital mortality. However, by 6 months, survival in the glutamine–treated group was significantly greater than in the control group (*p*=0.049). In another study of parenteral glutamine, Powell-Tuck at al[23] randomized 168 hospitalized patients with gastrointestinal failure who were receiving TPN to receive glutamine supplementation or placebo. Although the study did not demonstrate any statistically significant differences, it did suggest a trend towards a reduction in mortality associated with glutamine supplementation. Despite the fact that only one-quarter of these patients were actually cared for in a critical care environment, the mortality rate in the control group was 25% and approximated the mortality rate of the other ICU studies. O'Riordain et al[24] investigated the effect of glutamine on immune functions in surgical patients and in this clinically randomized study, demonstrated that glutamine supplementation therapy increases the mitogenic response of T cells. Sacks[25] carried out a meta-analysis of clinical studies on Medline published in English between January 1970 and December 1997. It has been reported that glutamine supplementation is efficacious for the patient group who are under stress, but further study is essential.

The most comprehensive Medline study on this subject was published by Novak et al in 2002.[26] The relation between glutamine supplementation therapy and hospitalization time, complication rates and mortality was studied in critically ill or surgical patients. Fourteen randomized studies, in which glutamine supplementation therapy could be compared to controls, were investigated. It was found that infectious complications decrease, and hospitalization times shorten in glutamine-treated patients in the surgical group, but that mortality rates remain as they are. It has been observed in critically ill patients that glutamine supplementation may also decrease the mortality rates. Similarly, our study established that hospitalization time and amelioration process were shortened, but there was no significant decrease in mortality rates, possibly due to the small number of patients. Although the mortality rate was reduced, the lack of significance may be due to the small number of patients.

In a paper by Oudemans-Van Straaten et al,[27] the relation of lower plasma glutamine levels to severity of illness and mortality was studied. Eighty patients were examined in this prospective cohort study, and patients whose plasma glutamine levels were <0.420 mmol/l were accepted as having lower glutamine levels. As a result, lower glutamine levels were correlated with older age, increase in mortality and a precursor of shock.

All these studies show that glutamine may contribute to good results especially by facilitating the immune system. Some studies have been designed to establish how much glutamine should be given and in which manner. In our study, it was administered intravenously in high doses, in parallel with other studies in the literature.

In conclusion, the results of the present study show that parenterally administered glutamine supplementation therapy in critically ill patients shortens the hospitalization time and fastens the amelioration process. It does not, however, affect mortality rates. Further study is essential on this subject.

References

1. Goeters C, Wenn A, Mertes N, Wempe C, Aken VH, Stehle P, et al. Parenteral L-Alanyl, L-Glutamine improves 6-month outcome in critically ill patients. *Crit Care Med* 2002; 30: 2032-2037.
2. Montejo JC. Enteral nutrition related gastrointestinal complications in critically ill patients: A multicentre study. *Crit Care Med* 1999; 27: 1447-1453.
3. Andrews FJ, Griffiths RD. Glutamine: Essential for immune nutrition in the critically ill. *Br J Nutr* 2002; 87: 3-8.
4. Wernerman J, Hammarqvist F. Glutamine: A necessary nutrient for the intensive care patient. *Int J Colorectal Dis* 1999; 14: 137-142.
5. Wilmore DW, Shabert JK. Role of glutamine in immunologic responses. *Nutrition* 1998; 14: 618-626.
6. Blomqvist BI, Hammarqvist F, Von der Decken A. Glutamine and alpha-ketoglutarate prevent the decrease in muscle free glutamine concentration and influence protein synthesis after total hip replacement. *Metabolism* 1995; 44: 1215-1222.
7. Planas M, Schwartz S, Arbos MA, Farriol M. Plasma glutamine levels in septic patients. *JPEN J Parenter Enteral Nutr* 1993; 17: 299-300.

8. Buchmann AL, Moukarzel AA, Bhuta S, Belle M, Ament ME, Eckhert CD, et al. Parental nutrition is associated with intestinal morphologic and functional changes in humans. *J Parenter Enteral Nutr* 1995; 19: 453-460.
9. Buchmann AL. Glutamine: A conditionally required nutrient for the human intestine? *Nutrition* 1997; 13: 240-241.
10. Hammarqvist F, Wernermann J, Ali R. Addition of glutamine to total parental nutrition after elective abdominal surgery spares free glutamine in muscle, counteracts the fall in muscle protein synthesis and improves nitrogen balance. *Ann Surg* 1989; 209: 455-461.
11. Ogle CK, Ogle JD, Mao JX, Simon J, Noel JG, Li BG, et al. Effect of glutamine on phagocytosis and bacterial killing by normal and pediatric burn patient neutrophils. *JPEN J Parenter Enteral Nutr* 1994; 18: 128-133.
12. O'riordain MG, De Beaux A, Fearon KC. A glutamine on immune function in the surgical patient. *Nutrition* 1996; 12: 82-84.
13. Amores-Sanches MI, Medina MA. Glutamine is a precursor of glutathione and oxidative stress. *Mol Genet Metab* 1999; 67: 100-105.
14. Houdijk AP, Rijnsburger ER, Jansen J, Wesdorp RI, Weiss JK, McCamish MA, et al. Randomised trial of glutamine-enriched enteral nutrition on infectious morbidity in patients with multiple trauma. *Lancet* 1998; 352: 772-776.
15. Newsholme P, Curi R, Pithon Curi TC, Murphy CJ, Garcia C, Pires de Melo M. Glutamine metabolism by lymphocytes, macrophages and neutrophils: it is importance in health and disease. *J Nutr Biochem* 1999; 10: 316-24.
16. Griffiths RD, Allen KD, Andrews FJ, Jones C. Infection, Multiple organ failure, and survival in the intensive care unit: Influence of glutamine- supplemented parental nutrition on acquired infection. *Nutrition* 2002; 18: 546-552.
17. Ardawi MS. Effect of glutamine enriched total parental nutrition on septic rats. *Clin Sci* 1991; 81: 215.
18. Li J, King BK, Janu PG, Renegar KB, Kudsk KA. Glycyl-L-Glutamine–enriched total parental nutrition maintains small intestine gut – associated lymphoid tissue and upper respiratory tract immunity. *JPEN J Parenter Enteral Nutr* 1998; 22: 31.
19. Mc Andrew HF, Lloyd DA, Rintala R, Van Saene HK. Intravenous glutamine or short chain fatty acids reduce central venous catheter infection in a total parental nutrition model. *J Pediatr Surg* 1998; 34: 281-282.
20. Jensen GL, Miller RH, Talabiska DG, Fish J, Gianferante L. A double-blind prospective randomized study of glutamine–enriched compared with standard peptide based feeding in critically ill patients. *Am J Clint Nutria* 1996; 64: 615-617.
21. Ziegler TR, Bye RL, Persinger RL, Young LS, Antin JH, Wilmore DW. Effects of glutamine supplementation on circulating lymphocytes after bone marrow transplantation: a pilot study. *Am J Med Sci* 1998; 315: 4-10.
22. Griffiths RD, Jones C, Palmer TE. Six-month outcome of critically ill patients given glutamine-supplemented parental nutrition. *Nutrition* 1997; 13: 295-302.
23. Powell-Tuck J, Jamieson CP, Bettany GE, Obeid O, Fawcett HV, Archer C, et al. A double blind, randomised, controlled trial of glutamine supplementation in parenteral nutrition. Gut 1999; 45: 82-88.
24. O'Riordain MG, Fearon KC, Ross JA, Rogers P, Falconer JS, Bartolo DC, et al. Glutamine-supplemented total parenteral nutrition enhances T-lymphocyte response in surgical patients undergoing colorectal resection. *Ann Surg* 1994; 220: 212-221.
25. Sacks G. Glutamine supplementation in catabolic patients. *Ann Pharmacotherapy* 1999; 33: 348-354.
26. Novak F, Heyland KD, Avenell A, Drover JW, Su X. Glutamine supplementation in serious illness: A systematic review of evidence. *Crit Care Med* 2002; 30: 2022-2030.
27. Oudemans-Van Straaten HM, Bosman RJ, Treskes M, Van der Spoel HJ, Zandstra DF. Plasma glutamine depletion and patient outcome in acute ICU admissions. *Intensive Care Med* 2001; 27: 12-15.