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COMPARISON OF ORAL VERSUS INTRAVENOUS GLUTAMINE IN CRITICALLY ILL PATIENTS

Anesthesiology

Konsam Jina Devi Senior Resident, Department of Anaesthesiology, RIMS, Lamphelapt, Imphal

Kangjam Sholay Meitei* Associate Professor, Department of Surgery, JNIMS, Porompat, Imphal *Corresponding Author

ABSTRACT

Objective: Since endogenous production of glutamine is reduced during critical illness and is a prognostic marker of sepsis, we studied the effect of glutamine therapy on biochemical parameters and the hospital stay of critically ill patients.

Methods: Sixty patients who were admitted to intensive care unit were randomly divided into: Group 1 (received no glutamine), Group 2 (received oral glutamine), and Group 3 (received L-alanyl-L-glutamine dipeptide). Total leukocyte count (TLC), total lymphocyte count, total protein and serum albumin, serum lactate, and sequential organ failure assessment (SOFA) score were recorded on each day for 7 days and were compared.

Results: Decrease in the TLC, increase in lymphocyte count, decrease in serum lactate and increase in serum protein and albumin was most evident in Group 3 compared to Groups 2 and 1.

Conclusion: Parenteral glutamine in a dose of 0.3 g/kg/d was more potent than oral glutamine in improving the biochemical parameters.

KEYWORDS

Glutamine, Serum lactate, Sepsis.

INTRODUCTION

Glutamine is a non-essential amino acid that can become conditionally essential under catabolic states such as critical illness and burns[1]. It is synthesized by the enzyme glutamine synthetase from glutamate and ammonia predominantly by muscle but also in small amounts by the lung and brain. It plays a central role as a fuel source for enterocytes, lymphocytes, and other rapidly dividing cells of the immune system[2]. Studies have shown that low plasma glutamine values on admission are related to increased mortality[3]. These findings are the rationale for the use of glutamine supplementation in the intensive care unit (ICU) patients to meet the demand for improvement in protein synthesis, modulation of the immune system, reduction of oxidative stress, and preservation of the gut barrier Some studies are there stating parenteral nutrition may be better than enteral nutrition in terms of clinical outcome in patients getting parenteral nutrition. The objective of this study was to evaluate the effect of parenteral glutamine and oral glutamine in critically ill patients. The primary objective of our study was to measure changes in the biochemical parameters such as total leukocyte count (TLC), lymphocyte count, serum protein and serum albumin and serum lactate levels. The secondary objective was to measure the effect on duration of hospital stay and mortality.

METHODS

This was a prospective randomized, single-blinded, placebo controlled study done at central ICU, IMS, BHU, Varanasi, between July 2013 and June 2014 after due permission from the hospital ethical committee. This study was done on 60 patients of age 18-70 years who were critically ill. Reason of ICU admission, i.e., medical reasons (respiratory failure, CVA, Urosepsis), elective surgery (major abdominal surgery, major thoracic surgery, and spine surgery), or emergency surgeries (perforation peritonitis, polytrauma). Patients with APACHE II score from 10 to 20 and expected stay in ICU>7 days were included in this study. Patients having renal failure, pregnancy, hepatic failure, patients receiving cytotoxic drugs, steroids and radiation therapy, unable to tolerate enteral feed within 72 hrs of admission and patients with gastrointestinal bleeding or intestinal obstruction were excluded from the study. The patients were divided into three groups of 20 each. Demographic variables were age, gender, and weight. APACHE II score at the time of admission, baseline hematological counts, serum electrolytes, serum protein, albumin, bilirubin, lactate, serum urea, and creatinine levels were recorded. The study groups received the following supplementation: Group 1 (Control): Received standard enteral feed along with 100 ml normal saline infusion. Group 2 (Enteral glutamine): received standard enteral feed along with 20g/day of glutamine along with 100 ml of normal saline infusion. Group 3 (Parenteral glutamine): received standard enteral feed along with 0.3 g/kg/day of IV glutamine as an infusion. The TLC, lymphocyte count, total platelet count, serum protein, serum albumin, serum urea, serum creatinine, serum bilirubin, serum lactate, and blood glucose were sent every morning at around 7 am. Sequential organ failure assessment (SOFA) score was assessed every day from day 1 to day 7.

The primary outcomes studied were the effect of glutamine supplementation on serum lactate, TLC, total serum lymphocyte count, serum protein and albumin and SOFA score. The secondary outcomes studied were the length of stay (LOS) in ICU, days of mechanical ventilation and mortality in ICU. The change in serum lactate level was used as primary endpoint .Statistical analysis was performed using SPSS 20 software. The values were described as mean±standard deviation if normally distributed and as median and interquartile range if the distribution is skewed. Age, weight, and APACHE II score were analyzed by ANOVA. The discrete variables, i.e., sex and mortality were analyzed using Chi-square or Fischer's exact test. The biochemical and clinical outcome parameters were analyzed by Kruskal–Wallis test. $p<0.05$ was considered significant. $p<0.001$ was considered as highly significant.

RESULTS

The improvement in laboratory parameters within each group was analyzed by comparing the median values of each parameter on days 1, 4 and 7 by Friedman test. In Group 1, there was no significant change in serum lactate level. There was a significant improvement in SOFA score in Group 1 between days 1 and 7, other values being statistically insignificant (Table 1).

Table 1: Comparison of parameters in Group 1

Variables	Day 1	Day 4	Day 7	p
Total leukocyte count (thousand/cm2)	9.23±1.62	9.94±1.34	8.44±0.95	0.061
Lymphocyte count (thousand/cm2)	2.82±0.42	2.58±0.64	2.60±0.55	0.195
Protein (g/dl)	5.77±0.15	6.40±0.19	5.18±0.22	0.580
Albumin (g/dl)	2.94±0.06	2.63±0.09	2.55±0.08	0.385
Serum lactate (mmol/l)	2.84±0.08	3.25±0.29	2.67±0.11	0.727
SOFA score	6.00±0.12	4.00±0.31	3.50±0.18	<0.001

In Group 2, the lymphocyte count increased appreciably from day 1 to day 7 but did not attain statistical significance. Serum albumin also increased markedly in Group 2 but not statistically significant. There was no significant change in serum lactate level, but there was a statistically significant improvement in SOFA score within the group in 7 days (Table 2).

Table 2: Comparison of parameters in Group 2

Variables	Day 1	Day 4	Day 7	p
Total leukocyte count (thousand/cm2)	12.61±1.34	11.18±1.10	10.10±1.85	0.834
Lymphocyte count (thousand/cm2)	2.09±0.34	1.97±0.25	2.42±0.52	0.142
Protein (g/dl)	5.56±0.64	5.55±0.75	5.64±0.82	0.422
Albumin (g/dl)	2.44±0.04	2.91±0.06	3.52±0.09	0.075

Serum lactate (mmol/l)	2.98±0.01	2.92±0.04	2.9±0.03	0.280
SOFA score	6.00±0.15	5.00±0.19	2.50±0.12	<0.001

In Group 3, there was statistically significant improvement in serum lactate, leukocyte count, lymphocyte count, and serum albumin and protein from day 1 to day 7. Improvement in SOFA score from day 1 to day 7 was statistically highly significant (Table 3). The mortality in the ICU between the groups was analyzed suing Fischer's exact test. The mortality rate in the parenteral group was lesser when compared to the control or enteral group but not statistically significant. The LOS in ICU and duration of mechanical ventilation was analyzed using Kruskal–Wallis test. The median LOS was 19.5 days in Group 1, 17 days in Group 2, and 19 days in Group 3 but not significant statistically.

Table3: Comparison of parameters in Group 3

Variables	Day 1	Day 4	Day 7	p
Total leukocyte count (thousand/cm2)	14.97±1.96	12.84±1.74	10.49±1.42	0.035
Lymphocyte count (thousand/cm2)	1.76±0.5	1.83±0.43	2.3±0.18	0.031
Protein (g/dl)	6.10±0.89	6.00±0.41	6.17±0.65	0.045
Albumin (g/dl)	2.97±0.02	3.34±0.06	3.43±0.09	0.042
Serum lactate (mmol/l)	3.05±0.01	3.07±0.03	2.97±0.01	0.04
SOFA score	6.00±0.12	4.50±0.16	2.00±0.24	<0.001

DISCUSSION

Nutrition has an important role in all ICU patients to combat the increased demand, maintain the basal function as well as to increase the immunological response. Enteral route is preferred due to its efficacy, safety, beneficial effect on gut function, and reduced side effects as compared to the parenteral route. Glutamine as an immune nutrient is recommended mainly in classes of patients such as burns and trauma. However, several published meta-analyses have initially showed a significant reduction in mortality and morbidity. Hence, we studied the effect of enteral and parenteral glutamine supplementation in critically ill patients from a mixed medical and surgical ICU. The optimal dose of glutamine by enteral route is still unknown, but studies have safely used up to 0.5 g/kg/day[3]. Up to 40 g/day of L-glutamine is safe by combined enteral and parenteral route[5]. Heyland *et al*. recommended that at least 6 days of parenteral therapy with glutamine in therapeutic dose was required to derive maximum benefit[6]. So in our study, we used a dose of 0.3 g/kg/day for a duration of 7 days. Day 1 SOFA score is an indicator of the severity of illness. In our study, the day 1 SOFA score median values were same in the three groups. However, the decrease in SOFA score from day 1 to day 7 was more in Group 3 as compared to 1 and 2. Our study reflected an increased improvement in SOFA score in the parenteral group than in the enteral group which is similar to study by Ferreira *et al.* [6]. This may be due to the delay in onset of action in the enteral glutamine group which may be due to impaired absorption in the intestinal villi, presence of immature villi, decreased blood flow in the gut, larger utilization by the enterocytes or metabolism by the splanchnic organs. The bioavailability of parenteral glutamine is 100%. This is consistent with the result of Beale *et al.* [8].

There was no significant change among the three groups with respect to the total leucocyte count, but the change was significant for total lymphocyte count on days 4 and 7. There was an improvement in lymphocyte count in both Groups 2 and 3 but reached significant levels only Group 3. This is consistent with the result of Fuentes-Orozco *et al.* who did not observe any difference in the total leukocytes count[9]. In our study, there was a significant increase in albumin levels in Group 3 although the Group 2 also showed some improvement in serum albumin. Ockenga *et al*. also showed a significant increase in serum albumin in acute pancreatitis patients supplemented with parenteral glutamine. This is particularly important in Indian population who are prone to malnutrition and hypoproteinemia, an important predictor of morbidity and mortality in hospitalized patients[10]. There was no significant difference in the mortality among the three groups. The number of deaths in Group 3 was lesser but not statistically significant. The LOS in ICU and duration of mechanical ventilation as predictors of morbidity was not statistically significant among the three groups.

Meta-analysis by Chen *et al.* showed no benefit of glutamine on mortality or LOS although there was a reduction in infection in the glutamine-supplemented group[11]. Meta-analysis by Kang *et al*. to assess the effect of glutamine in surgical patients with GI tumors showed improved immune function, reduce infections and shortened the length of ICU stay. John and Aanandhi, in their study, have concluded that the supplementation of enteral glutamine in post-operative patients decreases the incidence of post-surgical infection, shortening of hospital stay, and reduction in the overall hospital costs which were similar to our study[12]. Oktavia *et al*. in a review of many studies in critically ill adults suggested that glutamine-supplemented amino acid solutions may reduce mortality, improve nitrogen balance, and reduce the incidence of clinical infection[13]. Despite this apparent paradigm change, there is sufficient evidence in the literature on the benefits of glutamine that impel us to continue research by putting forth new questions.

CONCLUSION

It is not easy to obtain a clear answer to the above-quoted question, as the critically ill population is a heterogeneous one. Studies often mix patients with different pathologies and prognoses, as well as include distinct routes of administration and the use of different doses than those recommended by the guidelines, thus giving mixed results, especially when compared to a meta-analysis. The effect of parenteral glutamine supplementation on mortality differed with patient population, mode of nutrition, and glutamine dosages. There are differences in subpopulations of ICU patients with a beneficial improvement in the surgical population versus medical or mixed ICU population. Future research must explore the mechanism by which a glutamine deficiency could be harmful for some patients and how to supplement both dose and route.

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