A Comparative Study Of The Parenteral Glutamine And Oral Glutamine On Biochemical Parameters, Effect In Diminishing The Duration Of Intensive Care Stay, Mortality And Morbidity In Critically Ill Patients

D Singh, J S Bogra, V Bhatia, A Chaudhary, S Bhushan, Z Arshad, G Chandra, A Agarwal, S Saxena

Abstract
Objective: To study the effect of parenteral glutamine therapy on biochemical parameters, diminishing the hospital stay, mortality and morbidity.
Study design: Randomized Controlled trial.
Study site: Trauma Ventilatory Unit, Trauma Centre, KGMU, Lucknow.
Study subjects: 120 Critically ill patients aged 16 - 60 years being admitted to Trauma Ventilatory Unit, Trauma centre KGMU, Lucknow.
Methods: Patients were divided into 3 groups, 40 in each group: Group A (control group): No glutamine administration, Group B received Oral glutamine 20g/d for 5 days and Group C received l- alanyl – l - glutamine dipeptide 3g/kg/bw per day intravenous infusion for 5 days. Complete blood count was done at regular intervals of 24 hours. Total proteins and albumin were recorded at 5 day interval. Single blinding was done.
Results: The total leukocyte counts (TLC) levels in all the three groups increased after the treatment and the observed increase was evident least in Group C (18.7%) followed by Group B (32.5%) and Group A the highest (38.2%) increase. Almost similar observation was found for C Reactive Protein and lymphocyte levels in all three groups. However, a significant decrease was found in total protein and albumin levels. The mean duration of hospital stay of Group C was the least followed by Group B and Group A. infection among the three group, however, the incidence of infectious complication was least in group receiving parenteral glutamine as compared to other groups. Logrank test also revealed that the survival were similar (p>0.05) among the three groups
Conclusion: Parenteral glutamine in a dose of .3g/kg was more efficacious than 20g /day oral glutamine in increasing/decreasing in the biochemical parameters after the therapy. The duration of hospital stay was similar in all the groups after treatment.

INTRODUCTION
Glutamine is the most prevalent free proteic amino acid in the human organism. In the extracellular fluid, Glutamine constitutes approximately 25%, and in skeletal muscle more than 60% of the tissue amino acid free amino acid pool. Consequently, the transmembrane gradient over the muscle cell membrane is high, approximately 34:1 (intra: extracellular).1.

Free Glutamine concentrations diverge distinctly in various tissue pools with considerable differences between species in tissue free Glutamine concentrations. While it is often possible to make qualitative conjectures concerning human metabolism on the basis of animal studies, a quantitative understanding may require direct measurement of Glutamine in humans. Importantly plasma contains only a very small proportion of the free Glutamine pool. The main use of glutamine in the basal state as well as during critical illness is as an oxidative substrate. Endogenous production of glutamine may become insufficient during critical illness.
The rationale for treatment with glutamine supplementation in critically ill patients is the shortage of glutamine, the clinical evidence, and the fact that it is not harmful to patients. Grou et al (2011)3 in a multicenter, prospective, double-blind, randomized trial studied the clinical efficacy of alanine-Glutamine dipeptide-supplemented total parenteral nutrition defined by the occurrence of nosocomial infections.

Infection and sepsis are the main complicating factors leading to mortality and morbidity in patients admitted in intensive care unit. Although early death in intensive care unit from a single organ failure is usually due to the primary organ insult (e.g. trauma or sepsis) later death occurs due to multiple organ failure and is “associated” with the development of secondary infections. Although the intensity of the initial inflammatory response may correlate to tissue injury it is now appreciated that restoring an optimized immune system still capable of mounting a normal inflammatory signaling is a feature of survival. Glutamine is an example where a nutritional deficiency arises and whereby its correction improves survival from Multi Organ Failure (MOF). Garrel et al (2003)4 showed that a high risk of mortality population of patients with severe burns given enteral Glutamine showed a reduction in systemic infections and a significantly reduced intention-to-treat mortality rate. There was a low frequency of pneumonia, sepsis, and bacteremia in patients with multiple trauma who received Glutamine supplemented enteral nutrition2.

This study was conducted to compare the efficacy of parenteral glutamine and oral glutamine in critically ill patients to measure changes in biochemical parameters, in reducing the duration of stay, decreasing the mortality and morbidity in critically ill patients.

**METHODOLOGY**

The study was conducted on critically ill patients aged 16 - 60 years being admitted to Trauma Ventilatory Unit, Trauma centre KGMU, Lucknow from August 2011 to July 2012. The patients were randomly divided into following groups:

- **Group A** (control group) : No glutamine administration
- **Group B** : Oral glutamine 20g/d for 5 days
- **Group C** : L-alanyl – l - glutamine dipeptide 3g/kg/bw per day
  - intravenous infusion for 5 days

Group B was given enteral glutamine and group C was given parenteral glutamine. Baseline parameters were recorded at the time of admission. Complete blood count was done at regular intervals of 24 hours. Total proteins and albumin were recorded at 5 days interval along with blood culture and urine culture. Single blinding was done.

All the patients were monitored continuously for pulse rate, blood pressure (systolic, diastolic and mean), respiration and electrocardiography. All the patients undergoing study were investigated daily for total leukocyte counts, lymphocyte counts while total proteins serum albumin and C-reactive protein were measured on day 1 and day 5. The secondary efficacy variable such as length of hospital stay was also included. The incidence of infectious complication and mortality and morbidity were recorded.

**Ethical consideration**

The study was approved by the Institutional Ethical Committee of KGMU, Lucknow. The informed consent from each of the patients were taken before enrollment.

**Analysis**

Data were summarized as Mean ± SE. The outcome measures (lymphocyte count, total leukocyte count, C Reactive Protein, Total protein and Albumin) of three groups (Group A: Control, Group B: Oral Glutamine and Group C: IV Glutamine) were compared by two factor (Groups and Days) repeated measures analysis of variance (ANOVA) using general linear models (GLM) and the significance of mean difference within and between the groups was done by Newman-Keuls post hoc test. Age and Duration of hospital stay between the groups were compared by one factor ANOVA and the significance of mean difference between the groups was done by Newman-Keuls test. Survival between groups was evaluated by Logrank test. A two-sided (α=2) p<0.05 was considered statistically significant.

**RESULTS**

In all three groups, the proportion of males was higher than females. On comparing the sex proportion (M/F) between the three groups, χ2 test revealed similar (p>0.05) sex proportion between the three groups (M/F: 30/10 vs. 24/16 vs. 16/4, χ2=2.13; p=0.34). Among the three groups, the mean age of Group C was the highest followed by Group A and then Group B. On comparing the mean age of three groups, ANOVA revealed similar (p>0.05) age pattern between the three groups (F=2.46, p=0.09) (Table-1). The total leukocyte counts (TLC) levels in all the three groups increased after the treatment and the observed increase was evident least in Group C (18.7%) followed by
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Group B (32.5%) and Group A the highest (38.2%) increase. The C Reactive Protein levels in all three groups increased after the treatment and the increase was least evident in Group C (49.6%) followed by Group B (54.4%) and Group A with the highest (62.3%) value. The lymphocyte count levels in all three groups increased after the treatment and the increase was evident least in Group C (28.8%) followed by Group A (37.9%) and highest in Group B (41.0%). The increase in lymphocyte count from day 1 to day 5 was statistically significant (p<0.0001). The total protein levels in all the three groups also significantly decreased and the decrease was evident least in Group C (23.3%) followed by Group B (36.7%) and Group A with the highest increase (39.6%). The Albumin levels in all three groups decreased after the treatment and the decrease was evident least in Group C (5.3%) followed by Group B (16.1%) and Group A with the highest decrease (24.1%). The decrease was statistically significant (p<0.01) (Table-2).

The mean duration of hospital stay of Group C was the least followed by Group B and Group A. On comparing the mean duration of three groups, ANOVA revealed similar (p>0.05) hospital stay of all three groups (F=2.98, p=0.06). In other words, treatments did not change the duration of hospital stay (Fig.1).

The infection was least in Group C followed by Group B and Group A. However, all three groups showed UTI complications the most. On comparing the proportions of infectious complication among three groups, χ² test revealed similar (p>0.05) infection rates among the three groups (χ²=3.35; p=0.91) (Table-3).

The survival rate in Group C was the highest followed by Group B and Group A with the least. On comparing the survival proportion of three groups, χ² test revealed similar (p>0.05) survival proportion among the three groups (Live/Death: 22/10 vs. 26/14 vs. 16/4, χ²=2.85; p=0.2405). In other words, treatments did not change the survival (Table-4). Logrank test also revealed that the survival were similar (p>0.05) among the three groups (though it was higher in Group C as compared to both Group B and Group C (F=2.06, p=0.7185) (Fig.2).

### Table 1
Demographic profile of the patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Survival</th>
<th>Group B</th>
<th>Group C</th>
<th>χ², p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live</td>
<td>22 (59%)</td>
<td>26 (65%)</td>
<td>32 (80%)</td>
<td>2.05, 0.24</td>
</tr>
<tr>
<td>Death</td>
<td>18 (45%)</td>
<td>14 (35%)</td>
<td>8 (20%)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2
Day by day changes in the biochemical parameters (Mean ± SE) of three groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Day 1</th>
<th>Day 5</th>
<th>% mean change (Day 1-Day 5)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Reactive Protein levels (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>17.07 ± 0.25</td>
<td>25.76 ± 0.70</td>
<td>+52.5%</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Group B</td>
<td>16.54 ± 0.06</td>
<td>26.25 ± 0.55</td>
<td>+54.4%</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Group C</td>
<td>16.00 ± 0.05</td>
<td>20.63 ± 0.25</td>
<td>+45.0%</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Lymphocyte count (cells/µL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>14375 ± 2523</td>
<td>28435 ± 2034</td>
<td>+51.0%</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Group B</td>
<td>13060 ± 65.47</td>
<td>21750 ± 9279</td>
<td>+41.0%</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Group C</td>
<td>14850 ± 65.41</td>
<td>20795 ± 8368</td>
<td>+38.8%</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Serum protein levels (g/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>5.91 ± 0.12</td>
<td>6.22 ± 0.15</td>
<td>+5.0%</td>
<td>0.003*</td>
</tr>
<tr>
<td>Group B</td>
<td>6.06 ± 0.14</td>
<td>4.46 ± 0.10</td>
<td>-29.3%</td>
<td>0.000*</td>
</tr>
<tr>
<td>Group C</td>
<td>6.41 ± 0.16</td>
<td>5.20 ± 0.15</td>
<td>-21.4%</td>
<td>0.000*</td>
</tr>
<tr>
<td>Serum albumin levels (g/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>3.31 ± 0.08</td>
<td>3.57 ± 0.07</td>
<td>+7.6%</td>
<td>0.003*</td>
</tr>
<tr>
<td>Group B</td>
<td>4.08 ± 0.11</td>
<td>3.52 ± 0.05</td>
<td>-15.1%</td>
<td>0.000*</td>
</tr>
<tr>
<td>Group C</td>
<td>3.89 ± 0.09</td>
<td>3.70 ± 0.05</td>
<td>-6.1%</td>
<td>0.000*</td>
</tr>
</tbody>
</table>

*Significant

### Table 3
incidence of infectious complications

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Group A (n=40)</th>
<th>Group B (n=40)</th>
<th>Group C (n=40)</th>
<th>χ², p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTI</td>
<td>16 (40%)</td>
<td>14 (35%)</td>
<td>12 (30%)</td>
<td></td>
</tr>
<tr>
<td>UTI2</td>
<td>8 (20%)</td>
<td>6 (15%)</td>
<td>6 (15%)</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>16 (40%)</td>
<td>10 (25%)</td>
<td>4 (10%)</td>
<td></td>
</tr>
<tr>
<td>MCOB</td>
<td>4 (10%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4
Incidence of infectious complications

<table>
<thead>
<tr>
<th>Survival</th>
<th>Group A (n=40)</th>
<th>Group B (n=40)</th>
<th>Group C (n=40)</th>
<th>χ², p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live</td>
<td>22 (59%)</td>
<td>26 (65%)</td>
<td>32 (80%)</td>
<td>2.05, 0.24</td>
</tr>
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<td>18 (45%)</td>
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<td>8 (20%)</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1
Mean (± SE) Duration of hospital stay of three groups

DISCUSSION

This study was conducted to compare the efficacy of parenteral glutamine and oral glutamine. In our study, 120 patients were allocated to 3 different equal groups. The 3 groups were control (Group A), oral glutamine (Group B) and parenteral glutamine (Group C). Demographic data and duration of surgery was similar among the groups: mean age 38.05 ± 3.38 years, 35.40 ± 2.89 years and 44.70 ± 2.87 years in control group, oral glutamine group and parenteral glutamine group respectively.

We measured lymphocytes count on each day of the therapy in the three groups. The TLC levels in all three groups increased after the treatment and the increase was evident least in Group C (28.8%) followed by Group A (37.9%) and Group B with the highest increase (41.0%). Similarly the total leukocyte count levels in all three groups increases after the treatment and the increase was evident least in Group C (18.7%) followed by Group B (32.5%) and Group A the highest (38.2%). However, the TLC levels differed significantly (p<0.05) between Group A and Group C at day 2 and between all three groups (p<0.0001) at day 5. Keeping with this background, it is pertinent to speculate about the particular mechanism underlying the effect of glutamine dipeptide in causing reversal of the clinical and biochemical signs of critical illness. Obviously, there are distinct priorities of glutamine utilization during stress yet it is likely that the observed beneficial effects with supplemental glutamine are interrelated. The line of reasoning is supported by the fact that obvious beneficial effects on the immune system and GI tract can be achieved with low amount of supplemental glutamine5. In our study, total protein levels in all three groups decreased after the treatment and the decrease was evident least in Group C (23.3%) followed by Group B (36.7%) and Group A with the maximum (39.6%) decrease. Total protein levels did not differed (p>0.05) between the three groups at day 1 while at day 5 it differed significantly (p<0.001) between Group A and Group C (p=0.0002) and Group B and Group C (p=0.0009). This result was in contrast to study done by Griffith et al 19976 in which he found that there was no change in protein and albumin levels after treatment for five days with glutamine. Similar changes were studied by Sunil et al 20077 in studies of using glutamine enriched TPN in patients of acute pancreatitis. In the body, glutamine is used for the nitrogen requirements of immune system cells, enterocytes, and also for nitrogen resources of metabolic activities, and for filling the glutamine pool8-9. In some studies, it has been shown that TPN without glutamine had beneficial effects on the nitrogen balance like the glutamine enriched TPN10-11.

The level of CRP is the indicator of the most important biological function in the body, the role of which is to recognize and to stimulate the clearance of the cell remnants. In our study, the mean percent change in the CRP levels, from day 1 to day 5, increased in all the groups after the treatment. This increase was least evident in Group C (49.6%) followed by Group B (54.4%) and Group A the maximum increase (62.3%). At day 5, mean CRP level of Group C increased significantly (p=0.008) less as compared to Group A. The decrease in the treatment group was pronounced, but the values were still higher than the normal. The high CRP levels may be due to the presence of the
factors that affecting the CRP levels such as fever, leukocytosis and surgical operation as well as the presence of the inflammation. In a previous study investigating the effects of standard and glutamine-enriched PN on AP, CRP levels were determined for the evaluation of systemic inflammatory response, and CRP concentrations of the patients had decreased in the treatment group, whereas CRP level in the control group had decreased at the first week and increased thereafter. Glutamine is, generally, accepted as an immunomodulatory agent. In many studies performed on human and animals, glutamine has been beneficial effects on the immune system cells and their functions, thus reduction in infection rates was observed.

We measured lymphocytes count on each day of the therapy in the three groups. The LC levels in all three groups significantly increased after the treatment and the increase was evident least in Group C (28.8%) followed by Group A (37.9%) and Group B with the highest increase (41.0%). However, in some other studies, these effects have not been observed.

In our study, total protein and albumin levels in all three groups significantly decreased after the treatment and the decrease was evident least in Group C followed by Group B and Group A with the maximum decrease. Total protein levels did not differ (p>0.05) between the three groups at day 1 while at day 5 it differed significantly (p<0.001) between Group A and Group C (p=0.0002) and Group B and Group C (p=0.0009). This result was in contrast to study done by Griffith (1997) in which he found that there was no change in protein and albumin levels after treatment for five days with glutamine.

Several previous studies reported that glutamine supplementation to TPN shortens the length of hospital stay. In our study, the mean duration of hospital stay of Group C was the least followed by Group B and Group A.

Our study shows similar incidence of infection (p>0.05) among the three group however the incidence of infectious complication was least in group receiving parenteral glutamine. The number of patients died during the hospitalization was 9 in Group A, 7 in Group B and 4 in Group C. Among the surviving patients the duration of hospital stay was found to be maximum in group C. In predominantly septic multi-organ failure patients with non-functioning gastro-intestinal tracts six months survival was increased with glutamine to 57% from 33% in controls (p=0.049). It was promotion of recovery from infection and multiple organ failure that was most important rather than simply the prevention of infection although glutamine recipients do show a lower incidence of catheter-related infections (p=0.026). The difference in survival noted was almost all explained by reduced death within intensive care from MOF in those patients requiring a minimum of five days of parenteral feed (p=0.05).

In many studies performed on human and animals, glutamine has been beneficial effects on the immune system cells and their functions, thus reduction in infection rates was observed.

The frequency distribution of survival proportion (Live/Death) of three groups shows that the survival rate in Group C was the highest followed by Group B and Group A with the least. On comparing the survival proportion of three groups, \( \chi^2 \) test revealed similar (p>0.05) survival proportion among the three groups (Live/Death: 22/10 vs. 26/14 vs. 32/8; \( \chi^2=2.85; p=0.2405 \)). In other words, treatments did not change the survival among the three groups. Our results thus differ from a recent meta-analysis which strongly supports the hypothesis that parenteral glutamine has an advantageous effect on reducing mortality (RR=0.71, 95% CI=0.51-0.99). The meta-analysis confirms that glutamine via the enteral route has failed to show any effect on mortality (RR=1.08, 95% CI=0.57-2.01), but glutamine supplementation overall is associated with lower rates of infection (RR= 0.81, 95% CI=0.64-1.0).

Griffith (2000) investigated the effect of a Glutamine supplemented parenteral nutrition on Intensive Care Acquired Infection (ICAI) and its relation to outcome. Sepsis was present on admission in 71% of the patients. There was no significant difference in the number of patients developing new infections or in the number occurring during the first 5 days. There was a non-significant trend to increased numbers of infections in those patients receiving the control feed for at least 5 days. In these patients the Glutamine recipients showed significantly fewer catheter related infections: 21 versus 12 (p=0.02). The difference in overall 6-month mortality was almost completely described by those patients fed for at least 5 days. However, in another study of 84 ICU patients showed that by giving 14g Glutamine the incidence of new acquired infection was
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CONCLUSIONS

Parenteral glutamine in a dose of .3g/kg was more efficacious than 20g/day oral glutamine in increasing/decreasing in the biochemical parameters after the therapy. The duration of hospital stay was similar in all the groups after treatment. Our study also shows similar incidence of infection among the three group, however, the incidence of infectious was least in group receiving parenteral glutamine as compared to other groups and survival was higher and duration of stay was diminished.

References


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