The Effect of Administration of Intravenous Glutamine on the Infectious Morbidities in Severely Burn Patients on Enteral Nutrition in the Intensive Care Unit, a Randomized Controlled Trial

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Abstract

Background: Glutamine is an amino acid that has been shown to be beneficial for the metabolically stressed patient, especially the critically ill patients as it is important in modulation of immune cell function and production of cytokines. In this randomized controlled trial, we tested the effects of glutamine supplementation intravenously in severely burn patients receiving enteral nutrition in ICU on infectious complications, number of ventilator free days, number of days of antibiotic use and its effect on the routine blood tests.

Patients and Methods: Eighty two patients with burn more than forty percent of BSA in the ICU were randomized into two groups; Group G (glutamine group) and Group C (control group). Patients received continuous intravenous infusion of alanyl-glutamine (0.5g/kg/day) via central venous access until discharge from the ICU, death, or for maximum of 2 weeks and saline (2.5ml/kg/day) in Group C. SOFA score was calculated on admission and on the last day for each patient in the ICU. Rate of infection also was detected regarding surgical site, urinary tract, ventilator associated pneumonia and blood stream infection. We also monitored the ventilator free days and days of antibiotic use.

Results: Both groups had similar range of SOFA score (6-14), the mean was (0.07±1.96) in Group G and (0.12±1.54) in Group C, p=0.91. Number of days of using antibiotics was 6.1±1.8 in Group G and 6.9±1.3 in Group C, p=0.026. Number of ventilator-free days was 3.8±1.8 in Group G and 3.7±0.7 in Group C, p=0.687. Total leucocytic count was 8785±2937 in Group G and 13225±3273 in Group C, p=0.001. Platelets count was 136.9±33.7 in Group G and 136.8±34.5 in Group C, p=0.997.

Conclusion: In burn patients more than 40% in ICU on enteral nutrition, intravenous glutamine showed no effect neither on the SOFA scoring nor on the number of ventilator free days, but there was a significant decrease in the number of days of using antibiotics and the total leucocytic count and overall infectious morbidity.

Key Words: Glutamine – Burn – SOFA score – Ventilator free days – Antibiotics.

Introduction

METABOLISM and catabolism of glutamine in normal conditions: Glutamine is the most abundant free amino acid in the body and commonly known as a nonessential amino acid due to the ability of most cells to produce it [1]. Glutamine is present in the plasma at levels around 0.6mm and in the intracellular space at levels around 2 and 20mm [1].

It also serves as a metabolic intermediate, contributing carbon and nitrogen for the synthesis of other amino acids, nucleic acids, fatty acids, and proteins [2,3]. Glutamine through glutamate is a glutathione precursor, a tripeptide consisting of glutamate, glycine, and cysteine, with intracellular antioxidant capacity. Thus, its functions within the cell are generally separated into four categories: (1) Its role in nitrogen transport; (2) Its importance in maintaining the cellular redox state; (3) Its position as a metabolic intermediate; and (4) Its role as an energy source. Although some tissues use glutamine for one pathway more than others, glutamine metabolism occurs in all cells.

Metabolism and catabolism of glutamine during critical illness:

The expression of glutamine synthetase in mammalian systems is regulated mainly via two mechanisms: (A) Increased transcription in response to hormone action, and (B) Regulation of protein stability in response to glutamine concentration [3]. During physiologic stress, as sepsis, a rapid increase in plasma concentrations of cytokines and several classes of hormones, such as glucocorticoids, occurs.
Glutamine and the expression of heat shock proteins:

Glutamine's beneficial effects on critical illnesses may result from enhanced Heat Shock Proteins (HSP) expression expressed by leucocytes [4], monocytes, and granulocytes [5,6]. The heat shock proteins are a group of proteins essential to cellular survival under stressful conditions.

Glutamine and the development of acute lung injury/acute respiratory distress syndrome:

Critically ill patients are at high risk of glutamine depletion [7] and subsequent complications, such as the development of acute lung injury/Acute Respiratory Distress Syndrome (ARDS). Therapeutic interventions to improve outcomes from ALI/ARDS have met with limited success [8,9].

Severe burns covering more than 40% Total Body Surface Area (TBSA) are typically followed by a period of stress, inflammation, and hyper metabolism, characterized by a hyper dynamic circulatory response with increased body temperature, glycolysis, proteolysis, lipolysis, and futile substrate cycling [10].

All trauma, surgical, or critically ill patients, almost have the same reactions but the severity, length, and magnitude are unique for patients with burns [11]. Marked and sustained increases in catecholamine, glucocorticoid, glucagons, and dopamine secretion are believed to initiate the cascade of events leading to the acute hyper metabolic response with its ensuing catabolic state [12].

Attempting to overcompensate by providing excess calories and/or protein is ineffective and likely to increase such complications as hyperglycemia, CO2 retention, and azotemia. Thus, the primary goal of nutritional support in patients with burns is to satisfy acute, burn-specific requirements, and not to over feed. Under stress and catabolic conditions such as major surgery, there are a number of methods to determine the TBSA, including the Wallace rule of nines, Lund and Browder chart, and estimations based on a person's palm size. The rule of nines is easy to remember but only accurate in people over 16 years of age [13]. More accurate estimates can be made using Lund and Browder charts, which take into account the different proportions of body parts in adults and children [14]. The size of a person's handprint (including the palm and fingers) is approximately 1% of their TBSA [14].

The presence of systemic inflammatory response syndrome is defined by the finding of two or more markers of inflammation which include: (1) Temperature above 38°C or below 36°C, (2) Heart rate >90b.pm., (3) Respiratory rate >20min or PaCO2 >32mmHg and (4) WBC count of >12,000/mm³, or <4,000 mm³ or left shift with >10% bands. Although the precept of systemic inflammatory response syndrome has been widely accepted and applied by the critical care community [15].

The alterations in metabolism and physiology that accompany burn injury result in increased temperature, heart rate, respiratory rate and blood pressure. These changes render the definition of systemic inflammatory response syndrome far too inclusive to be useful for predicting the presence of infection or impending sepsis in burn patients [15].

Burn wound infection: The burn wound results in disruption of the normal barrier function of the skin rendering it highly susceptible to invasion by colonizing bacteria. Although the incidence of infection has declined, the list of offending microorganisms has not changed significantly [16].

Pneumonia: In general, the causative organisms of pneumonia in burn patients appears to be similar to that in other critically ill patients with hospital acquired pneumonia [17,18].

Blood stream infection: Is a well recognized complication of central venous catheters use. However, data suggests that patients with burn injury are at a much higher risk for central venous catheters colonization and central venous catheters related blood stream infection. There is evidence to suggest that placement of the central venous catheters adjacent to burned tissue increase the risk of catheter colonization and blood stream infection [13,15].

Material and Methods

The study is a prospective, interventional, single-centre, concealed block-randomization, triple-blinded (subject, care givers, outcome assessor), placebo-controlled trial, it was conducted from October 2012 to April 2015 in the ICU Unit at Kasr El-Eini Hospital, Cairo University after approval from the local ethical committee and obtaining written informed consent from all patients enrolled in the study.

Patients range between 18-85 years with severe burn more than 40%, required enteral feeding more
than 48 hours, length of stay in the ICU more than 48 hours, with functional access for enteral feeding and negative pregnancy test.

Patients should not be pregnant, neither less than 18 years nor more than 85 years, no significant hepatic or renal failure, no inborn error of metabolism or metabolic acidosis.

The glutamine group received intravenous alanyl-glutamine (0.5g/kg/day); by continuous infusion (24h/day) through a dedicated lumen via central venous access until discharge from the ICU, death, or for a maximum duration of 14 days while the control group received intravenous placebo (normal saline; 0.9% NaCl; 2.5ml/kg/day) by continuous infusion (24h/day) through a dedicated lumen via central venous access until discharge from the ICU, death or for a maximum duration of 2 weeks.

All patients in both groups received standard, polymeric, high-caloric, high-protein enteral formula (1.2kcal/1ml; 12g/l fibre; 55.5g/l protein) and start at a rate of 50ml/h according to the standard feeding protocol followed at the surgical ICU.

Enteral nutrition was initiated within 24-48h, and the aim was to reach the target goal by day 3. Parenteral nutrition was started when enteral nutrition has failed by day 7 post ICU admission.

SOFA score: Was measured on admission and on the last day of treatment, where the change in total SOFA score=baseline total SOFA score-last day of treatment total SOFA score. A higher number indicates an improvement compared with baseline.

Respiratory system:

<table>
<thead>
<tr>
<th>PaO2/FiO2 (mmHg)</th>
<th>SOFA score</th>
</tr>
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<tbody>
<tr>
<td>&lt;400</td>
<td>1</td>
</tr>
<tr>
<td>&lt;300</td>
<td>2</td>
</tr>
<tr>
<td>&lt;200 and mechanically ventilated</td>
<td>3</td>
</tr>
<tr>
<td>&lt;100 and mechanically ventilated</td>
<td>4</td>
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</tbody>
</table>

Nervous system:

<table>
<thead>
<tr>
<th>Glasgow coma scale</th>
<th>SOFA score</th>
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</thead>
<tbody>
<tr>
<td>13-14</td>
<td>1</td>
</tr>
<tr>
<td>10-12</td>
<td>2</td>
</tr>
<tr>
<td>6-9</td>
<td>3</td>
</tr>
<tr>
<td>&lt;6</td>
<td>4</td>
</tr>
</tbody>
</table>

Cardio vascular system:

<table>
<thead>
<tr>
<th>Mean arterial pressure or administration of vasopressors required</th>
<th>SOFA score</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP &lt;70mm/Hg</td>
<td>1</td>
</tr>
<tr>
<td>dop &lt;=5 or dob (any dose)</td>
<td>2</td>
</tr>
<tr>
<td>dop &gt;5 OR epi &lt;=0.1 OR nor &lt;=0.1</td>
<td>3</td>
</tr>
<tr>
<td>dop &gt;15 OR epi &gt;0.1 OR nor &gt;0.1</td>
<td>4</td>
</tr>
</tbody>
</table>

(Vasopressor drug doses are in µg/kg/min).

Drug abbreviations: Dop for dopamine, dob for dobutamine, epi for epinephrine and nor for norepinephrine.

Liver:

<table>
<thead>
<tr>
<th>Bilirubin (mg/dl) [µmol/L]</th>
<th>SOFA score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2-1.9 [20-32]</td>
<td>1</td>
</tr>
<tr>
<td>2.0-5.9 [33-101]</td>
<td>2</td>
</tr>
<tr>
<td>6.0-11.9 [102-204]</td>
<td>3</td>
</tr>
<tr>
<td>&gt;12.0 [&gt;204]</td>
<td>4</td>
</tr>
</tbody>
</table>

Coagulation:

<table>
<thead>
<tr>
<th>Platelets X 10^9 /µl</th>
<th>SOFA score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150</td>
<td>1</td>
</tr>
<tr>
<td>&lt;100</td>
<td>2</td>
</tr>
<tr>
<td>&lt;50</td>
<td>3</td>
</tr>
<tr>
<td>&lt;20</td>
<td>4</td>
</tr>
</tbody>
</table>

Renal system:

<table>
<thead>
<tr>
<th>Creatinine (mg/dl) [µmol/L] (or urine output)</th>
<th>SOFA score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2-1.9 [110-170]</td>
<td>1</td>
</tr>
<tr>
<td>2.0-3.4 [171-299]</td>
<td>2</td>
</tr>
<tr>
<td>3.5-4.9 [300-440]</td>
<td>3</td>
</tr>
<tr>
<td>&gt;5.0 [&gt;440] (or &lt;200ml/d)</td>
<td>4</td>
</tr>
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</table>

2- Infectious morbidity in the form of:

- Urinary tract infection or catheter related infection was diagnosed by urine culture.
- Central line insertion related infection or blood stream infection was diagnosed by a single blood culture for organisms not commonly present on the skin and two or more blood cultures for organisms commonly present on the skin) in a patient who had a central line at the time of infection or within the 48-hour period before development of infection.
- Ventilator Associated Pneumonia (VAP) was diagnosed by a new infiltrate on chest X-ray plus two or more other factors. These factors include temperature of >38°C or <36°C, a white blood cell count of > 12 X 109/ml, purulent secretions from the airways in the lung, and/or reduction in gas exchange.
3- The number of Ventilator-Free Days (VFD) and days of antibiotic use during the ICU stay were recorded.

4- Routine ICU blood tests were daily withdrawn and recorded until discharge from the ICU, including white-blood-cell count, platelets, neutrophils, lymphocytes, monocytes, urea, creatinine, protein and albumin.

Statistical analysis:

Statistical analysis was performed using PASW soft-ware version 19.0 (SPSS). A baseline comparison of demographics, severity of illness and baseline measures was carried out between each group, using a combination of student \( t \)-tests and \( \chi^2 \) tests. Dichotomous data as ICU mortality and in hospital mortality was compared between groups using the \( \chi^2 \) test. Normally distributed continuous data was analyzed by a parametric test (i.e, student \( t \)-test or ANOVA) and reported as mean ± SD. Non-normally distributed continuous data was analyzed with an appropriate non-parametric test (e.g, Mann e Whitney test) and reported as median ± IQR.

Data was analyzed on the basis of intention-to-treat analysis (as per randomization) and per protocol analysis for patients who received at least 5 days supplementation. The differences was considered statistically significant at \( p \leq 0.05 \). An intention-to-treat analysis using a carry-forward analysis for missing data was performed for all participants including withdrawn patients.

Results

Regarding the demographic data, there was no significant difference was found between both groups regarding age, weight, BMI and percentage of burn.

Table (1): Demographic data and percentage of burn in both groups.

<table>
<thead>
<tr>
<th></th>
<th>GLN group</th>
<th>Control group</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: Mean ± SD</td>
<td>39.9±13.2</td>
<td>45.2±16.1</td>
<td>0.111</td>
</tr>
<tr>
<td>Range</td>
<td>19-65</td>
<td>19-78</td>
<td></td>
</tr>
<tr>
<td>% of burn:</td>
<td>52.1±8.44</td>
<td>53.5±8.15</td>
<td>0.2</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>40-73%</td>
<td>40-80%</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>22-46</td>
<td>20-50</td>
<td></td>
</tr>
<tr>
<td>BMI:</td>
<td>34.5±5.6</td>
<td>35.7±6.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Concerning the infectious morbidity, in the Glutamine group, in the form of significant decrease in the Total Leucocytic Count (TLC) in blood samples withdrawn as there was a marked decrease in the incidence of VAP detected by Endo Tracheal Aspirate (ETA) and Broncho Alveolar Lavage (BAL), a marked decrease in the number UTIs detected by urine cultures and a significant decrease in the incidence of bloodstream infection detected by negative blood cultures. No significant difference
in the blood tests done in the form of serum albumin, platelets' count, serum creatinine and urea between both groups.

Discussion

Early trials of GLN were primarily focused on patients receiving full nutrition support primarily by PN at doses falling within the approved prescribing indications for dose in commercially available GLN preparations. Further, patients in these traditional trials were commonly excluded from enrollment if they had pre-existing renal or liver failure. These traditional nutritionally oriented (or non pharmaco-nutrition based) GLN supplementation trials have shown a consistent reduction of mortality and benefit on other outcomes as suggested by the 2009 update of the Canadian Critical Care Nutrition Guidelines [19].

However, given the publication of 11 new randomized controlled trials examining the traditional parenteral use of GLN as a component of nutrition support (predominantly PN) since 2009, a new systematic review is indicated. This need for a new systematic review is further driven by the results of the REDOXS (REduced Deaths due to Oxidative Stress) trial, a 1,200-patient, 40-center randomized controlled trial of 'pharmacologically dosed' parenteral and enteral GLN (approximately 0.6 to 0.8 g/kg/day) factorialized with antioxidant supplementation [19].

This trial was distinct from any of the previously published parenteral GLN trials supplementing PN or EN in ICU patients as GLN (and a cocktail of antioxidants) were administered independent of any concomitant nutrition support. In contrast to the design of studies reported in this analysis, the nutritional delivery of energy and protein in the REDOXS trial averaged less than 50% of that prescribed for the patient, and thus was quite insufficient in meeting patient needs [18].

A number of studies [20] have shown beneficial effects of GLN given enterally or as a supplement to parenteral nutrition in seriously ill patients, BUT this study differs for two reasons:

A- It used intravenous GLN as a pharmacologic intervention (in addition to standard enteral nutrition support) rather than as a supplement to total parenteral nutrition; and,

B- It examined the effect of GLN in severely burned patients. Enteral nutrition has become the preferred method of feeding in severely burned patients because there are fewer infections compared with parenteral feeding [19,21].

Furthermore, enteral feeding is thought to preserve gut barrier function and prevent gut atrophy more effectively than parenteral nutrition. However, studies in critically ill patients that use oral GLN supplements have not consistently shown increases in plasma GLN concentration. As a result, we administered the GLN supplement as a continuous intravenous infusion. GLN supplementation was well tolerated in both groups. However, these data are consistent with the results of a previous trial of GLN in multiply traumatized patients [20,21]. That study demonstrated a statistically significant reduction in the incidence of bacteremia, septic episodes, and pneumonia in GLN-treated patients vs. an iso nitrogenous control.

The results of our study and the study of multiple trauma patients support the hypothesis that GLN may enhance gut barrier function and prevent bacterial translocation from the gut. Neither trial was designed to specifically examine this, and so no clear conclusions can be drawn. The results of our study suggest that GLN decreases the overall systemic inflammatory response, which may be related to the relative decrease in bacteremia in GLN-treated patients. Another explanation is that GLN may directly affect the release of pro inflammatory cytokines [22].

Despite the attenuation of infectious morbidity and systemic inflammation and the improvement in nutritional parameters, no significant decrease \( p > 0.05 \) in over all mortality, (VFD) Ventilator Free Days, platelets count and albumin level [19,21]. A larger trial would be necessary to critically examine the effect of GLN on mortality.

The strength of our study includes the use of several methods to reduce bias (comprehensive literature search, duplicate data abstraction, specific criteria for searching and analysis) and focus on clinically important primary outcomes. Not with standing, we are aware that it had several limitations. The major limitation is the small sample size. Another potential weakness of any systematic review of randomized controlled nutrition trials has been pointed out by Vincent et al., recently [22].

Conclusion:

We have shown that GLN treatment given as a supplement to standard enteral nutrition decreases the incidence of Gram-negative bacteremia, attenuates measures of overall inflammation, and improves nutritional status in severely burned patients but no effect on the overall mortality.
The Effect of Administration of Intravenous Glutamine on the Infectious Morbidities

References


المملوک العربي

تمثل الحروق الشديدة مشكلة كبيرة في جميع أنحاء العالم. عادة ما يسبح هذه الحروق الشديدة التي تغطي أكثر من 40% إجمالي مساحة سطح الجسم فترة من الإجهاد، والالتهابات، وتستجيبًا للعوامل المفرطة مثل حرارة الجسم، مع تحلل البروتينات الدهنية والكربوهيدرات.

في مواجهة ذلك، هناك استمرار مستويات الجلوتامين في العشائر. على الرغم من أن إنتاج الجلوتامين هو زيادة في المستويات في الحالات الحرجة، فإننا ليس كافياً للحفاظ على مستويات الخلايا من الجلوتامين في العشائر.

على جهاز التنفس الصناعي، وتقليل عدد أيام استخدام العظام الجراحية خلال إقامة المريض في وحدة الرعاية المركزية، في تقليل عدد الوظائف في المستشفى في مقارنة مع الدواء الوعائي لمرضى الحروق الشديدة في الرعاية المركزية.

أجريت هذه الدراسة لتحديد ما إذا كان اختلاف الجلوتامين عن طريق الوريد (5 جم/كجم/اليوم) سيؤدي إلى تحسين النتائج السريرية للمرضى مثل تحسن أجهزة الجسم الشعاعية وتقليل مدة الإقامة في وحدة الرعاية المركزية.

ولكن لم يكن هناك اختلاف ملحوظ في المجموعة التي تم إعطائها الجلوتامين الوردي عن مجموعة التحكم من حيث تحسن وظائف أجهزة الجسم، مدة الإقامة في وحدة الرعاية المركزية ونسبة الوفيات في المستشفى بعد الخروج من الرعاية المركزية.

لا يوجد اختلاف كبير في وفيات المستشفيات بين المجموعتين:

• انتفاخ ملحوظ في إجمالي عدد كرات الدم البيضاء.
• انتفاخ ملحوظ في مزارع الدم الموجبة.
• انتفاخ ملحوظ في عدد الالتهابات الرئوية الناتجة عن أجهزة التنفس الصناعية في مجموعة الجلوتامين.
• انتفاخ ملحوظ في عدد من عدوى السعال البولية الناتجة عن القضاة البولية في مجموعة الجلوتامين.

(أ) هناك تباين كبير في الحالات المرضية المعدية في مجموعة الجلوتامين مقارنة مع مجموعة التحكم في صورة:

• انتفاخ ملحوظ في إجمالي عدد كرات الدم البيضاء.
• انتفاخ ملحوظ في مزارع الدم الموجبة.
• انتفاخ ملحوظ في عدد الالتهابات الرئوية الناتجة عن أجهزة التنفس الصناعية في مجموعة الجلوتامين.
• انتفاخ ملحوظ في عدد من عدوى السعال البولية الناتجة عن القضاة البولية في مجموعة الجلوتامين.