Introduction

Glutamine is an important fuel that is used by the intestinal mucosa, immunological cells, and other rapidly proliferating tissue. Recent investigations have shown that glutamine provides a major portion of the energy required by mucosal cells and that it is an important oxidative fuel for enterocytes. Our previous studies demonstrated that enteral nutrition with glutamine was beneficial in minimizing intestinal mucosal injury by lessening the intestinal translocation of bacteria and endotoxin in burned rats. However, few studies have demonstrated these responses to glutamine supplementation in human patients after burn injury. The main aim of this study is to examine the protective effect of glutamine granules on the intestinal mucosal barrier function in severely burned patients and its mechanism.

Materials and methods

Patients and groups

Forty-eight patients with severe burns in our hospital's Institute of Burn Research were included in the study, of whom 29 were males and 19 females. The age range was from 18 to 60 yr (mean, 36.48 ± 11.44 yr). The total body surface area (TBSA) burned ranged from 30 to 75% (mean, 50.95 ± 10.51%); full-thickness burns ranged from 20 to 58% (mean, 31.74 ± 8.49%). All the patients were admitted within 24 h post-burn injury and there were no cases of severe inhalation injury or cardiovascular and renal disease. The patients were randomly divided into a glutamine group (GLN, n = 25) and a burn control group (B, n = 23), supplemented respectively with 0.5 g/kg daily glutamine granules and placebo (0.5 g/kg daily glycine). The glutamine granules were provided by Chongqing Yao You Pharmaceutical Ltd. Burn patients received 180 kJ/kg daily and 2.0 g/kg daily protein with non-protein energy in a glucose nitrogen ratio of 150:1. There was no difference in the average caloric and nitrogen intake. Both groups received similar conventional therapy after admission. The normal controls (n = 10) were selected from students (18-22 yr) at our university. All control subjects were healthy and without any history of recent or remote gastrointestinal tract, cardiovascular, or renal disease.

The study protocol was approved by the Ethics Committee of our University, and informed consent was obtained from all subjects or their family.

Plasma glutamine concentration

The plasma glutamine concentration was quantitated by using high-pressure liquid chromatography. The detailed method has been previously described.

Plasma Diamine oxidase (DAO) activity

Plasma Diamine oxidase DAO activity was assessed according to the modified method of Nobumichi et al.

Intestine mucosal permeability

Intestine mucosal permeability was assessed by the lactulose-mannitol ratio in urine. Urine volume was measured and the concentration of lactulose and mannitol were determined according to the method of Kingstone et al.

Plasma endotoxin level

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ANALYSIS OF EFFICACY AND SAFETY OF GLUTAMINE GRANULES IN SEVERELY BURNED PATIENTS


Institute of Burn Research, Southwestern Hospital, Third Military Medical University, Chongqing, People's Republic of China

SUMMARY. In order to evaluate the clinical therapeutic effect and safety of glutamine granules on severe burn patients, 48 severely burned patients were randomly divided into two groups: a burns control group (B group, 23 patients) and a glutamine granules treatment group (GLN group, 25 patients). The GLN group patients were given glutamine granules 0.5 g/kg daily for 14 days and the B group received the same dosage of placebo for 14 days. The plasma glutamine concentration, the degree of intestinal mucosa damage, blood biochemistry, and complications were observed. The results show that after 14 days of oral administration of glutamine granules, the plasma glutamine concentration in the GLN group was significantly higher than in the B group (p < 0.01). The degree of intestinal damage and intestinal mucosa permeability in the GLN group was lower than that in the B group. This indicates that orally supplemented glutamine could reduce the degree of intestinal injury and lessen intestinal mucosal permeability. There was no evidence of any side effects.
The plasma endotoxin level was assessed by the end-point chromogenic method based on the activation of a limulus amoebocyte lysate heparin. The limulus kits were provided by Sigma Chemical Co., and manipulation was performed according to the instructions in the kits.

**Statistical analysis**

All values were expressed as mean ± SEM. Groups of data were compared using Student’s t-test for unpaired data or with an analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparison tests. The frequency of burn surface, age, and sex were evaluated using the χ² test. Values of p < 0.05 were regarded as significant, and p < 0.01 as very significant.

**Results**

**Patients and treatment**

During the period April 2001-January 2003, 48 patients with severe burns were admitted to our Institute of Burn Research (GLN group, n = 25; B group, n = 23). There were no differences between groups as regards age, gender ratio, TBSA, or percentage of third-degree burns (p > 0.05) (Tables I, II). Patients with inhalation injury or requiring mechanical ventilation on admission were excluded from the study.

**Table I** - Sex and age of patients in the two groups

<table>
<thead>
<tr>
<th>Sex and age (yr)</th>
<th>B group</th>
<th>GLN group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>15</td>
<td>14</td>
<td>1.0000</td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
<td>11</td>
<td>0.6846</td>
</tr>
<tr>
<td>18-20</td>
<td>3</td>
<td>3</td>
<td>1.0000</td>
</tr>
<tr>
<td>21-40</td>
<td>13</td>
<td>15</td>
<td>0.8199</td>
</tr>
<tr>
<td>41-60</td>
<td>7</td>
<td>7</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

**Table II** - Area and depth of burns

<table>
<thead>
<tr>
<th></th>
<th>B group</th>
<th>GLN group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBSA (%)</td>
<td>48.32 ± 10.62</td>
<td>53.45 ± 9.48</td>
<td>0.1441</td>
</tr>
<tr>
<td>Full-thickness burns (%)</td>
<td>29.84 ± 8.89</td>
<td>33.55 ± 7.66</td>
<td>0.2003</td>
</tr>
</tbody>
</table>

**Changes in plasma glutamine concentration after burn injury**

Plasma glutamine levels were decreased in all the burn patients compared with normal controls (p < 0.01). Glutamine granule supplement (0.5 g/kg) daily for 14 days reversed the changes, bringing glutamine levels near to normal controls (p > 0.05). In B group patients, with supplemented placebo, plasma GLN levels continued to decrease. Results in the GLN group were significantly higher than those in the B group (p < 0.01) (Table III).

**Changes in plasma DAO activity after burn injury**

**Table III** - Changes in plasma glutamine concentration

<table>
<thead>
<tr>
<th>Group</th>
<th>Before treatment</th>
<th>After 14 days' treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group (n = 10)</td>
<td>615.58 ± 88.79</td>
<td>615.58 ± 88.79</td>
</tr>
<tr>
<td>B group (n = 23)</td>
<td>397.36 ± 159.58b</td>
<td>447.42 ± 132.38b</td>
</tr>
<tr>
<td>GLN group (n = 25)</td>
<td>407.31 ± 152.70b</td>
<td>607.86 ± 147.23c</td>
</tr>
</tbody>
</table>

a p < 0.01 vs Control group; b p < 0.01 vs before treatment; c p < 0.01 vs

Plasma DAO activity was significantly higher after burn injury, and glutamine administration decreased DAO activity. It was only 66.34% of the B group, i.e. a significant change (p < 0.01). It was however still higher than that of normal controls (p < 0.01) (Table IV).

**Changes in serum endotoxin after burn injury**

Serum endotoxin levels were significantly higher in both groups than those in normal controls (p < 0.01). Compared with the B group, values in the GLN group were markedly decreased after administration of glutamine granules for 14 days (Table IV).

**Changes of urinary lactulose and mannitol concentrations and lactulose/mannitol ratio**

Urinary lactulose concentrations were significantly higher in burn patients than in normal controls post-burn (p < 0.01). Compared with the B group, GLN group values were markedly decreased after administration of glutamine granules for 14 days (p < 0.01). There was no significant difference in mannitol excretion between the two groups. The lactulose/mannitol ratio in the B group was significantly higher than that of GLN groups (p < 0.01) (Table IV).

**Table IV** - Changes in intestinal mucosal barrier function

<table>
<thead>
<tr>
<th>Index</th>
<th>Control group (n = 10)</th>
<th>Before treatment</th>
<th>After placebo use for 14 days</th>
<th>GLN group (n = 25)</th>
<th>Before treatment for 14 days</th>
<th>GLN treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAO (IU/ml)</td>
<td>0.25 ± 0.12</td>
<td>2.83 ± 1.72b</td>
<td>2.05 ± 0.82b</td>
<td>3.07 ± 1.88a</td>
<td>1.36 ± 0.48bc</td>
<td></td>
</tr>
<tr>
<td>L/M (%)</td>
<td>0.03 ± 0.01</td>
<td>0.26 ± 0.09b</td>
<td>0.20 ± 0.06b</td>
<td>0.25 ± 0.06a</td>
<td>0.12 ± 0.09bc</td>
<td></td>
</tr>
<tr>
<td>Endotoxin</td>
<td>0.06 ± 0.02</td>
<td>0.35 ± 0.12b</td>
<td>0.21 ± 0.07b</td>
<td>0.37 ± 0.13a</td>
<td>0.13 ± 0.05bc</td>
<td></td>
</tr>
</tbody>
</table>

a p < 0.01 vs C group; b p < 0.01 vs before treatment; c p < 0.01 vs B group
glutamine was the principal fuel utilized by enterocytes and that glutamine was able to stimulate mucosal cell proliferation by promoting protein and nucleic acid production.\(^2\) Glutamine could minimize injury and promote repair of the intestine.

The present study found that serum endotoxin levels were significantly higher in both burn groups than in normal controls \((p < 0.01)\). Compared with the B group, the GLN group was markedly decreased after use of glutamine granules for 14 days, although the level was still higher than in normal controls. The results showed that glutamine supplementation was able to maintain intactness of the intestinal barrier and reduce the plasma endotoxin level.

Why is glutamine so important for the intestine? Glutamine is an important energy source in gut mucosa and a principal fuel substrate for enterocytes. Gore et al.\(^3\) reported that more than 55% of vitamins were extracted by the small intestine after burn injury and that the uptake increased after critical illness and surgical stress, contributing to glutamine depletion.\(^4\) We found that plasma glutamine concentration was significantly decreased after burn injury and that supplementary glutamine was able to reverse this change.

**Conclusion**

These results show that orally administered glutamine can increase plasma glutamine concentration and improve glutamine metabolism. We found that supplementary glutamine significantly relieved the degree of intestinal injury and decreased plasma DAO activity, the endotoxin level, and the urine lactulose/mannitol ratio. Our study also shows that an increased plasma concentration of glutamine due to oral administration of glutamine granules is possible. These findings argue strongly in favour of the use of enteral supplementary glutamine as a benefit for severe burned patients.

**RÉSUMÉ.** Dans le but d'évaluer l’effet thérapeutique clinique et la sécurité des granules de glutamine dans le traitement des grands brûlés, 48 patients sévèrement brûlés ont été divisés au hasard en deux groupes: un groupe témoin de patients brûlés (groupe B, 23 patients) et un groupe de patients traités avec des granules de glutamine (groupe GLN, 25 patients). Le groupe des patients GLN recevait des granules de glutamine 0.5 g/kg par jour pour 14 jours et le groupe B recevait le même dosage de placebo pour 14 jours. La concentration de la glutamine plasmatique, le degré du dommage intestinal et de la perméabilité de la muqueuse intestinale dans le groupe GLN était supérieur en manière significative à celui du groupe B \((p < 0.01)\). Le degré du dommage intestinal et de la perméabilité de la muqueuse intestinale dans le groupe GLN était inférieur à celui du groupe B. Ce résultat indique que la glutamine oralement supplémentée pourrait réduire le degré des lésions intestinales et la perméabilité muqueuse intestinale. Les Auteurs n'ont observé aucun effet secondaire.

**BIBLIOGRAPHY**


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**G. WHITAKER INTERNATIONAL BURNS PRIZE-PALERMO (Italy)**

**Under the patronage of the Authorities of the Sicilian Region for 2005**

By law n. 57 of June 14th 1983 the Sicilian Regional Assembly authorized the President of the Region to grant the Giuseppe Whitaker Foundation, a non profit-making organisation under the patronage of the Accademia dei Lincei with seat in Palermo, a contribution for the establishment of the annual G. Whitaker International Burns Prize aimed at recognising the activity of the most qualified experts from all countries in the field of burns pathology and treatment.

Law n. 23 of December 2002 establishes that the prize becomes biannual. The next prize will be awarded in 2005 by the month of September in Palermo at the seat of G. Whitaker Foundation.

The amount of the prize is fixed at Euro 20,660.00.

The Adjudicating Committee is composed of the President of the Foundation, the President of the Sicilian Region, the Representative of the Accademia dei Lincei within the G. Whitaker Foundation, the Dean of the Faculty of Medicine and Surgery of Palermo University, the President of the Italian Society of Plastic Surgery, three experts in the field of prevention, pathology, therapy and functional recovery of burns, the winner of the prize awarded in the previous year and a legal expert nominated in agreement with the President of the Region as a guarantee of the respect for the scientific purpose which the legislators intended to achieve when establishing the prize.

Anyone who considers himself/herself to be qualified to compete for the award may send by January 31st 2005 a detailed curriculum vitae to: Michele Masellis M.D., Secretary-Member of the Scientific Committee G. Whitaker Foundation, Via Dante 167, 90141 Palermo, Italy.