A Randomized Trial of Glutamine and Antioxidants in Critically Ill Patients

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• Critically ill patients have **oxidative stress**
• The most seriously ill patients have increased mediators of oxidant stress and a higher incidence of multiorgan failure
• **glutamine** and **antioxidant supplementation** in critically ill patients may be associated with improved survival?
Methods

• Study Participants
  – receiving mechanical Ventilation
  – included if they had two or more organ failures related to their acute illness
Study Design and Interventions

• glutamine/placebo solution
  – glutamine supplementation (0.35g/kg/day, intravenously according to ideal body weight)
  – provided as 0.50g/kg/day iv of the dipeptide alanyl-glutamine [Dipeptiven, Fresenius Kabi] and 42.5g/day enterally of alanyl-glutamine and glycine-glutamine dipeptides, which provide (30 g of glutamine)
• IV+enteral minerals+vitamins/placebo
  – IV: 500µg selenium (Selenase, Biosyn)
  – Enteral:
    • 300 µg of selenium
    • 20 mg of zinc
    • 10 mg of beta carotene
    • 500 mg of vitamin E
    • 1500 mg of vitamin C
• Administered for a maximum of 28 days
• The primary outcome: 28-day mortality
• The study was conducted according to the protocol
• April 2005 to December 2011
• 40 ICUs in participating countries
Results—Patients

• There were 1218 patients in the final intention-to-treat analysis
5633 Patients were assessed for eligibility

4410 Were excluded
3350 Did not meet eligibility criteria
   1045 Were admitted to ICU after 24 hr
   518 Had absolute contraindication to enteral nutrients
   419 Had severe acquired brain injury
   295 Were not expected to stay in ICU > 48 hr
   237 Had Child–Pugh class C cirrhosis
   238 Lacked commitment to full aggressive care
   163 Had life expectancy of < 6 mo
   142 Had seizure disorder requiring anticonvulsant
   95 Underwent routine elective cardiac surgery
   81 Weighed < 50 kg or > 200 kg
   70 Were enrolled in related ICU interventional study
   19 Were pregnant or lactating with intent to breast-feed
   15 Had diagnosis of burns (≥30% BSA) at primary admission
   9 Underwent previous randomization in the study
   1 Was < 18 yr of age
   3 Had other reasons

1060 Were eligible, but did not undergo randomization
   471 Did not have family present
   233 Declined to participate
   180 Were expected to stay in ICU < 5 days
   82 Were overlooked by investigators
   39 Were withdrawn by physician
   55 Had other reasons

1223 Underwent randomization
1223 Underwent randomization

- 302 Were assigned to receive placebo
  - 1 withdrew consent before initiation of study supplements
  - 1 withdrew consent after 3 days on study
  - 300 were included in the primary analysis
- 303 Were assigned to receive glutamine
  - 2 withdrew consent before initiation of study supplements
  - 301 were included in the primary analysis
- 308 Were assigned to receive antioxidants
  - 1 withdrew consent before initiation of study supplements
  - 307 were included in the primary analysis
- 310 Were assigned to receive antioxidants plus glutamine
  - 310 were included in the primary analysis
Primary Outcome

• The overall 28-day mortality was 29.8%
• No significant interaction between glutamine and antioxidants
• no significant differences in 28-day mortality in any of our a priori subgroup analyses in the intention-to-treat analysis
Secondary Outcomes

- In-hospital mortality and mortality at 6 months were significantly higher among patients who received glutamine.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Glutamine</th>
<th>No Glutamine</th>
<th>P Value</th>
<th>Antioxidants</th>
<th>No Antioxidants</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death — no. of patients/total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>At day 28</td>
<td>198/611 (32.4)</td>
<td>165/607 (27.2)</td>
<td>0.05*</td>
<td>190/617 (30.8)</td>
<td>173/601 (28.8)</td>
<td>0.48</td>
</tr>
<tr>
<td>At day 14</td>
<td>157/611 (25.7)</td>
<td>129/607 (21.3)</td>
<td>0.07</td>
<td>154/617 (25.0)</td>
<td>132/601 (22.0)</td>
<td>0.23</td>
</tr>
<tr>
<td>In hospital</td>
<td>227/611 (37.2)</td>
<td>188/607 (31.0)</td>
<td>0.02</td>
<td>216/617 (35.0)</td>
<td>199/601 (33.1)</td>
<td>0.51</td>
</tr>
<tr>
<td>At 6 mo†</td>
<td>259 (43.7)</td>
<td>218 (37.2)</td>
<td>0.02</td>
<td>242 (40.4)</td>
<td>235 (40.6)</td>
<td>0.87</td>
</tr>
</tbody>
</table>
• Significant increases in the median time to discharge alive from the ICU and the median time to discharge alive from the hospital among patients who received glutamine

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<tbody>
<tr>
<td>Time from randomization to final discontinuation of mechanical ventilation and alive — days‡</td>
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<tr>
<td>Median</td>
<td>11.0</td>
<td>8.7</td>
<td>0.03</td>
<td>9.1</td>
<td>10.5</td>
<td>0.67</td>
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<tr>
<td>Interquartile range</td>
<td>4.0–undefined</td>
<td>3.9–58.8</td>
<td></td>
<td>3.9–undefined</td>
<td>4.0–undefined</td>
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<tr>
<td>Time from randomization to discharge alive from ICU — days‡</td>
<td></td>
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</tr>
<tr>
<td>Median</td>
<td>17.1</td>
<td>13.1</td>
<td>0.03</td>
<td>15.1</td>
<td>14.0</td>
<td>0.34</td>
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<tr>
<td>Interquartile range</td>
<td>7.3–undefined</td>
<td>7.1–undefined</td>
<td></td>
<td>7.2–undefined</td>
<td>7.2–undefined</td>
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<tr>
<td>Time from randomization to discharge alive from hospital — days‡</td>
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</tr>
<tr>
<td>Median</td>
<td>51.0</td>
<td>40.1</td>
<td>0.04</td>
<td>43.8</td>
<td>42.7</td>
<td>0.39</td>
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<tr>
<td>Interquartile range</td>
<td>17.9–undefined</td>
<td>16.3–undefined</td>
<td></td>
<td>18.0–undefined</td>
<td>16.2–undefined</td>
<td></td>
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</tbody>
</table>
Secondary Outcomes

• Glutamine vs no glutamine: no significant effect on the outcomes of organ failure or infections

• Antioxidant vs no antioxidants: no significant effect on secondary outcome
Adverse Events

- 52 serious adverse events in 46 patients
- 4 considered potentially related to study supplements
- The frequency of high urea levels (>50 mmol/L) was higher among patients who received glutamine than among those who did not (13.4% vs. 4.0%, P<0.001)
Laboratory Substudy

- Glutamine vs no glutamine: significant increase in plasma glutamine levels on day 4 and 7
- Antioxidant vs no antioxidants: significant increase in plasma selenium levels on days 4 and 7
Discussion

• Glutamine:
  – nonsignificant increase in 28-day mortality
  – significant increases in in-hospital and 6-month mortality
  – No effect on any other outcome

• Antioxidants:
  – not associated with any effect on study outcomes
Discussion-Glutamine

• Glutamine may cause harm?
  – prior meta-analysis of smaller, less methodologically robust trials
  – patients in our trial received the highest dose
  – iv and enteral supplementation
  – critically ill patients w/ multiorgan failure
  – Initiate study supplements within 24 hours
  – most of our patients received enteral nutrition
Discussion-Glutamine

• Our view and hypothesis
  – rapid depletion of plasma glutamine levels in critical illness
  – furthermore, lower plasma glutamine levels have been associated with increased mortality
  – critically ill patients with organ dysfunction have low plasma glutamine levels
  – would benefit the most from supplements
Discussion-Glutamine

• We did not consistently find a deficiency of glutamine in the substudy involving 66 patients.
Discussion-Antioxidants

• no effect overall or in any subgroup?
  – characteristics of the study population, dose, method of administration
  – insufficient dose of selenium or used an ineffective dosing schedule
Discussion-Strength

- Randomized and blinded design,
- rigorous determination
- adjudication of infection
- intention-to-treat analysis
- high rate of adherence to trial interventions
- large number of patients
- enrollment in ICUs in North America and Europe
Discussion-conclusion

- Early administration of glutamine in critically ill patients with multiorgan failure was harmful
- The majority of these patients did not have glutamine deficiency early in their critical illness
- Antioxidant supplementation as provided in this trial conferred no therapeutic benefit