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Effect of intravenous GLutamine supplementation IN Trauma patients receiving enteral nutrition (GLINT Study): a prospective, blinded, randomised, placebo-controlled clinical trial

Dr. Ruqaiya Moosa Al Balushi
Assistant Professor
Nutrition & Health Department
United Arab Emirates University
Adjunctive supportive Role

Therapeutic Intervention

"It's your four basic food groups."

Immune-modulating Nutrients

Glutamine
Nucleic Acids
Arginine
Omega-3 Fatty Acids

Pharmaconutrition: a new emerging paradigm
Naomi E. Jones\textsuperscript{a,b} and Daren K. Heyland\textsuperscript{a,b,c}

**Old Immunonutrition**
- Combination of nutrients
- Low doses
- Heterogeneous population
- Weak, underpowered trials
- Surrogate outcomes

**New Pharmaconutrition**
- Single/ key nutrients
- Pharmacologically safe doses
- Homogeneous population
- Well designed trials
- Major clinical outcomes
Pathophysiology of trauma

Trauma: Any physical damage to the body and often occurs in young patients, who have little or no protein depletion.
Immune Response of Trauma

Trauma insult

Pro-inflammatory cytokines

Anti-inflammatory cytokines

Uncomplicated trauma

Balanced

SIRS

Restore homeostasis

CARS

Imbalanced

Sepsis, MODS & MOF

DEATH

Immune-modulating nutrients (GLUTAMINE)

Adapted from Bone RC. Crit Care Med 1996;24(7):1125-1128
Physiology of GLN Metabolism

Most abundant amino acid in the body\(^1\)

Crucial substrate for numerous metabolic activities

60% of a.a. pool in skeletal muscle & 25% plasma free a.a.s\(^2\)

Considered non-essential a.a.

GLN Conditionally Essential amino acid in Critical Illness

- Major surgery\(^1\)
- Burn injury\(^2\)
- Multiple trauma\(^3\)

Plasma GLN levels

Conditionally essential amino acid\(^4\)

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GLN Therapy

- Decreased Free Radical Activity (anti-inflammatory action)
- Glutathione Synthesis
- Enterocyte Fuel
  - Maintenance of Gut Barrier
  - Reduced Bacteria Translocation
  - Reduced infectious complications
  - Enhanced HSP induction
  - Tissue Protection
- Nucleotide Synthesis
- Lymphocyte Fuel
  - Maintenance of Immune Function

Glutamine, a life-saving nutrient, but why?*
Crit Care Med 2003 Vol. 31, No. 10

The glutamine story: where are we now?
Paul E. Wischmeyer
Current Opinion in Critical Care 2006, 12:142-148

Glutamine in Critical Illness: The Time Has Come, The Time Is Now
Lindsay-Rae B. Weitzel, PhDa,*, Paul E. Wischmeyer, md b
EN Gln supp.
Limitations

- Less systemic bioavailability
- Difficulty to reach target dose
- Uncertain absorption

IV GLN Supp.
GLN Trial Limitations in Critical Illness

- Rarely Assessed Gut function
- Population heterogeneity (recommendations diff.)
- Inconsistent feeding regimen
- Underpowered for primary outcomes
- Short Period of Supp. (e.g. 7 days)
- Inability to deliver suppl. enteral feed (intolerance)
- Require large # of participants
- Different trials used different doses
- Mixture of immunonutrients as intervention

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• Gln supp. has demonstrated improved clinical outcomes in patients receiving total parenteral nutrition\textsuperscript{1-3}

• The results of Gln in patients receiving EN are conflicting and inconclusive\textsuperscript{4-6}

• The Role of IV Gln in a homogenous population of multiple trauma patients has not been discussed extensively in the literature

• The GLINT trial is the first trial to investigate the effect of IV Ala-Gln supp. in a pharmacological dose (0.5g/kg) in trauma patients receiving EN on organ failure, infectious complications & body composition.


Objective

• Determine the effect of IV Ala-Gln in multiple trauma patients receiving enteral nutrition on reducing organ failure, infectious complications and body composition
Research questions?

• Effect of IV Ala-Gln in trauma patients receiving EN on organ dysfunction; (ΔSOFA).

• Effect of IV Ala-Gln on infectious morbidity, ICU & Hospital length of stay, VFD, number of days of antibiotic use during ICU stay, Body composition?
Significance

First clinical trial to investigate effect IV suppl. of Alanyl-GLN in multiple trauma patients receiving EN on:

- Organ dysfunction.
- Body composition.
Inclusion criteria

1. Age 18-85 years
2. Multiple trauma req. mechanical ventilation.
3. Requiring EN > 48 hrs
4. Expected ICU length stay > 48 hrs.
5. Has functional access for EN and central access for test soln.
6. Negative Beta HCG (pregnancy test) in females (18-60 years)
Exclusion criteria

1. Age < 18 years
2. Significant hepatic failure (Childs C Cirrhosis)
3. Severe renal failure (glomerular filtration rate [eGFR] < 50 ml/min.
4. Inborn errors of a.a. metabolism
5. Metabolic acidosis (pH < 7.35)
6. Not expected to be in ICU > 48 hrs (due to imminent death)
7. Unable to tolerate EN within 72 hrs.
8. Enrolment in other ICU intervention if contraindicated.
9. PN required from outset.
10. Absolute contraindication to EN.
11. Transferred to another institute before fifth day after onset of supp.
Methodology

- **Setting:** ICU at Royal Brisbane and Women’s Hospital (RBWH).
- Thirty multiple trauma patients receiving EN were recruited in this prospective, double-blinded, randomised, placebo-controlled clinical trial to receive either 0.5 g/kg/day IV Ala-Gln or IV placebo (0.9% NaCl) by continuous infusion (24 hr/day).
- Both groups received the same standard EN protocol and the same standard ICU care for a maximum duration of 3 weeks.
- This trial has been approved by the University of Queensland Human Ethics Committee & the Human Ethics Committee of RBWH.
Trial Flowchart

Assessed for eligibility
N = 155

n = 125 excluded

n = 30 Randomised

n = 15 Ala-Gln
(n= 1 adverse event )

n = 15 Control
(n= 1 did not receive supp., no CVC)
### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Ala-Gln</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Sex, Male, n (%)*</td>
<td>15 (100)</td>
<td>11 (78.6)</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>48 (18)</td>
<td>48 (14)</td>
</tr>
<tr>
<td>BMI (kg/m²)*</td>
<td>26.7 (5.6)</td>
<td>27.5 (7.5)</td>
</tr>
<tr>
<td>APACHE II*</td>
<td>16.9 (5.2)</td>
<td>16.6 (5.7)</td>
</tr>
<tr>
<td>ISS*</td>
<td>41 (32 – 41)</td>
<td>38 (32 – 41)</td>
</tr>
<tr>
<td>GCS*</td>
<td>9 (7 – 14)</td>
<td>11 (8 – 14)</td>
</tr>
<tr>
<td>SOFA score (Total)#</td>
<td>10 (7 – 11)</td>
<td>8 (6 – 9)</td>
</tr>
</tbody>
</table>

* P value = NS
# P value = 0.08
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Ala-Gln</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Prescribed Energy (Kcal/day)</td>
<td>2400 (2304 – 2880)</td>
<td>2400 (2304 – 2736)</td>
</tr>
<tr>
<td>Prescribed Protein (gm/day)</td>
<td>121 (106.6 – 133.2)</td>
<td>121 (106.6 – 126.5)</td>
</tr>
<tr>
<td>Prescribed Supp.(mL/day)</td>
<td>191 (16.2)</td>
<td>183.8 (24.8)</td>
</tr>
<tr>
<td>Supp. starting time (hrs)</td>
<td>35 (15 – 44)</td>
<td>40 (20 – 42)</td>
</tr>
</tbody>
</table>

P value = NS
## Supplementation and Enteral Feeding

<table>
<thead>
<tr>
<th></th>
<th>Ala-Gln</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Energy intake (Kcal/d)</td>
<td>1437 (876)</td>
<td>1224 (539)</td>
</tr>
<tr>
<td>Energy % from prescribed/day</td>
<td>60.9 (34.1 – 83.5)</td>
<td>56.7 (28.6 – 67.2)</td>
</tr>
<tr>
<td>Duration of supplementation (d)</td>
<td>9 (6)</td>
<td>8(5)</td>
</tr>
<tr>
<td>Patients had Supp. ≥ 5 days, n (%)</td>
<td>10 (71.4)</td>
<td>9 (64.3)</td>
</tr>
<tr>
<td>Supp. intake (ml/d)</td>
<td>153.5 (133.5 – 186.5)</td>
<td>147.5 (131.5 – 166.4)</td>
</tr>
<tr>
<td>Supp. % form prescribed/day</td>
<td>85.9 (71.8 – 95.7)</td>
<td>87.1 (71.3 – 90.9)</td>
</tr>
<tr>
<td>Pts. required jejunal tube, n(%)</td>
<td>0(0)</td>
<td>2 (14.3)</td>
</tr>
<tr>
<td>Pts. required TPN, n (%)</td>
<td>1 (7.1)</td>
<td>2 (14.3)</td>
</tr>
<tr>
<td>Pts. ≥ 1 diarrhea episodes</td>
<td>6 (42.9)</td>
<td>5 (35.7)</td>
</tr>
</tbody>
</table>

P value = NS
Figure 1: Change in estimated mean of $\Delta$ SOFA for groups from day 2–11. lb/ub, lower bound/upper bound.

(Regression coefficient = 0.4938; 95% CI -0.8113 to 1.7988; p=0.46).
## Infectious complications & other secondary outcomes

<table>
<thead>
<tr>
<th></th>
<th>Ala-Gln (n=15)</th>
<th>Control (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infectious Complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAP, n (%)</td>
<td>2 (14.3)</td>
<td>6 (42.9)</td>
</tr>
<tr>
<td>Sinusitis, n (%)</td>
<td>1 (7.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Meningitis, n (%)</td>
<td>1 (7.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sepsis, n (%)</td>
<td>2 (14.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Days of antibiotic use in ICU</strong></td>
<td>0 (0 – 6)</td>
<td>5.5 (0 – 8)</td>
</tr>
<tr>
<td><strong>VFD (days)</strong></td>
<td>17 (16- 24)</td>
<td>22 (19 – 23)</td>
</tr>
<tr>
<td><strong>ICU length of stay (days)</strong></td>
<td>14 (6 – 16)</td>
<td>10 (6 – 12)</td>
</tr>
<tr>
<td><strong>Hospital length of stay</strong></td>
<td>41 (25)</td>
<td>48 (32)</td>
</tr>
</tbody>
</table>

P value = NS
Figure 2: Change in estimated mean urea level (mmol/L) in groups during the first 10 days. lb/ub, lower bound/upper bound

(Regression coefficient = -1.9652; 95% CI -3.0746 to -0.8557; p = 0.001)
Figure 3: Change in estimated mean creatinine level (µmol/L) in groups during the first 10 days. lb/ub, lower bound/upper bound

(Regression coefficient = -12.2301; 95% confidence intervals -21.8559 to -2.6042; p = 0.01)
Figure 4: The pattern of change in estimated mean FFM % in groups over two weeks. FFM, fat-free mass; lb/ub, lower bound/upper bound (p= 0.002) over 2 weeks

(regression coefficient = -5.5591; 95% CI -12.4765 to 1.3583; p = 0.12)
Figure 5: Estimated mean of log plasma lymphocyte count \((10^9/ \text{L})\) levels in groups during the first 10 days of supp.

(regression coefficient = 0.061; 95% confidence intervals -0.2139 to 0.3360; \(p = 0.66\))
Figure 6: Estimated mean of albumin levels in groups during the first 10 days of supplementation.

(regression coefficient = 0.3002; 95% confidence intervals -1.9981 to 2.59845; p = 0.8)
Adverse Events

• one patient with TBI in the Ala-Gln group developed refractory seizures and accordingly the supp. was ceased on day 11.

• Plasma glutamate level was above normal levels (110 umol/ L)

• Plasma glutamine level was low (380 umol/ L)

• Normal plasma level ranges are (420 – 700 umol/ L) for glutamine and (10 – 50 umol/ L) for glutamate.
Strengths

• First trial to investigate benefits of IV ala-Gln in multiple trauma pts receiving EN.
• Used the highset approved dose.
• Supp. through IV route → ensure receiving target prescribed dose.
• Long-term supp. (i.e. during ICU stay or max. 21 days)
Limitations

- The small sample size & single centre → a pilot trial.
- Not having a lower level for APACHE II or ISS for inclusion → resulted in including patients who were not very severely ill and thus received the supplementation for a short period.
- Pts relatively young with no previous co-morbidities.
- Did not investigate the underlying mechanisms. outcomes.
- Excluding patients with an eGFR < 50 resulted in excluding patients who were severely ill.
Limitations

• Using BIS as a measure of body.
• Omission of reporting plasma and intramuscular glutamine concentration at baseline and during supplementation.
• Not addressing the effect of glutamine supplementation on inflammatory markers (e.g. CRP & IL levels).
• Not using an isonitrogenous control which may have resulted in increased nitrogen intake in the Ala-Gln supplemented group.
Suggestion for Future Trials

• Future trials should enrol patients who are seriously ill and expected to stay for a prolonged duration in the ICU.

• If a quick test (i.e. within 24-48 hours) for plasma Gln levels on admission was feasible, the upcoming trials should select patients with depleted admission plasma glutamine levels.

• Supplementation should continue on discharge from the ICU to the ward.

• Investigate the effect of glutamine supplementation in elderly patients (i.e. > 65 years) as many of the previous trials excluded this population group.
Conclusion

• The benefits of IV Ala-Gln were not confirmed in this trial.
• The significant increase in urea and creatinine levels suggests further investigation about the safety of glutamine on renal function.
• Include severely ill patients in future trials & those a with glutamine depletion by applying screening for admission plasma glutamine levels.
• The focus of future trials should be on both the clinical outcomes and the underlying mechanisms of glutamine supplementation.
• A rigorous, multicenter trial is needed to confirm the efficacy of IV Ala-Gln in preserving lean-body mass in multiple trauma patients.
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