

Optimizing the Dose of Glutamine Dipeptides In Critically Ill Patients. A Phase I dose finding study of glutamine supplementation in critically ill patients

Synopsis

Overall Hypothesis: The provision of high dose glutamine to critically ill patients with evidence of hypoperfusion early in the course of their stay will be associated with improved survival.

Background: Critically ill patients experience a degree of hyperinflammation, cellular immune dysfunction, and oxidative stress. Glutamine supplementation is most likely to have a favourable effect on these physiological parameters leading to an improvement in clinical outcomes. The results of a meta-analysis suggested that higher doses of glutamine (>0.2gm/kg/day) may be associated with improved survival compared to lower doses (<0.2gm/kg/day). However, the optimal dose of glutamine is unknown. Existing safety data suggest that 0.5 gms/kg/day of Dipeptiven® intravenously is safe in critically ill patients. The highest total dose possible (enteral and parenteral combined) that does not produce unacceptable toxicity is unknown. The purpose of this study is to determine the safety and maximal tolerable dose (MTD) of glutamine dipeptides, provided intravenously as Dipeptiven® and enterally as Intestamin®, in critically ill patients with evidence of hypoperfusion.

Study Design: A single center, open-label, phase I dose ranging clinical trial with prospective controls

Setting: Kingston General Hospital (KGH), a tertiary care ICU in Ontario, Canada.

Study population: Mechanically ventilated adult patients (≥18 years old) admitted to ICU with clinical evidence of hypoperfusion. We will exclude patients who are underweight (<50 kgs) and those with severe head trauma (GCS <8 or need for ventriculostomy) due to safety reasons.

Study Intervention: Patients will be sequentially enrolled to one of 4 groups:

Group 1: Prospectively, we will identify 30 patients who meet study eligibility criteria to determine the baseline rate of study measurements including adverse events, organ function, and need for dialysis.

Group 2: The next 7 patients will receive a standard dose of Dipeptiven®, 0.5 gms/kg/day of glutamine dipeptides (0.35 grams/kg/day of glutamine) intravenously and nothing enterally.

Group 3: The next 7 patients will receive Dipeptiven®, 0.5 gms/kg/day of glutamine dipeptides (0.35 grams/kg/day of glutamine) intravenously and 21.25 grams/day of glutamine dipeptides (15 grams/day of glutamine) enterally provided as 250 ml of Intestamin® per day via nasogastric tube infusion;

Group 4: The next 7 patients will receive Dipeptiven®, 0.5 gms/kg/day of glutamine dipeptides (0.35 grams/kg/day of glutamine) intravenously and 42.5 grams/day of glutamine dipeptides (30 grams/day of glutamine) enterally provided as 500 ml of Intestamin® per day via nasogastric tube infusion.

Following initial resuscitation, dosing strategies will begin and will continue until nutrition support is discontinued, death, or discharge from ICU unless an individual patient has an adverse event related to study intervention or reaches a pre-determined safety threshold. The final safety thresholds will be determined after baseline data collected (Group 1) and analyzed. If 3/7 patients in a group (42%) reach the threshold of safety, then no further dosing increments will occur but an additional 5 patients will be evaluated at the previous dosing range. In the event the MTD is not reached at the highest dose level, then the protocol may be amended to include

further dose escalations. All patients will be fed according to clinical practice guidelines; enteral feeds will be initiated as per clinical practice.

Outcomes: The primary outcome for this study is change (delta) sequential organ failure assessment (SOFA score). The secondary outcomes are serum chemistries (BUN, AST, ALT, GGT, ammonia and plasma amino acid and dipeptide levels), tolerance of enteral nutrition, duration of mechanical ventilation, hospital length of stay, and 28 day mortality.

Sample Size and Duration: 30 patients (non-consented) in prospective cohort which serves as a control group and 21 patients prospectively enrolled in dose-ranging studies from KGH site over 6 months.

Significance: The therapeutic strategies tested in this randomized trial will illuminate optimal dose and duration for glutamine that will inform a large, multicenter, Phase III randomized trial of glutamine supplementation in critically ill patients (The REDOXS study).