

## OPTIMIZING THE DOSE OF GLUTAMINE DIPEPTIDES AND ANTIOXIDANTS IN CRITICALLY ILL PATIENTS: A PHASE I DOSE FINDING STUDY

D. K. Heyland\*<sup>1</sup>, R. Dhaliwal<sup>1</sup>, A. Day<sup>2</sup>, J. Drover<sup>3</sup>, H. Cote<sup>4</sup>, P. Wischmeyer<sup>5</sup>

<sup>1</sup>Department of Medicine, Queen's University, <sup>2</sup>Clinical Research Centre, Kingston General Hospital,

<sup>3</sup>Department of Surgery, Queen's University, Kingston, <sup>4</sup>Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, Canada, <sup>5</sup>Department of Anesthesiology, University of Colorado Health Sciences Center, Denver, United States

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**Rationale:** Higher doses of glutamine (GLN) and antioxidants may be associated with an improvement in clinical outcomes, yet the optimal dose of these nutrients is unknown. The purpose of this study was to determine the safety and maximal tolerable dose of GLN combined with antioxidants in critically ill patients.

**Methods:** We conducted a single center, open-label, dose ranging clinical trial. Mechanically ventilated adult patients with hypoperfusion were sequentially enrolled to one of 5 groups and received nutrients up to 21 days. Group 1 (n=30): no supplementation; Group 2 (n=7): 0.35 gms/kg/day of GLN intravenously (IV); Group 3 (n=7): 0.35 gms/kg/day of GLN IV and 15 gms/day of GLN and 150 ug of selenium enterally; Group 4 (n=7): same IV dose as Group 3 and 30 gms/day of GLN and 300 ug of selenium enterally; Group 5 (n=7): same as group 4 and 500ug of selenium IV.

**Results:** The primary outcome for this study was change in organ function score. Secondary outcomes included plasma levels of administered substrates, glutathione (GSH), thiobarbituric acid reactive substances (TBARS), interleukin-6 (IL-6), and mitochondrial DNA/nuclear DNA ratio (RATIO). Organ dysfunction was not significantly different across groups (p=0.19). In Group 2, a significant decrease in GSH levels was observed (p=0.03). With subsequent Groups, there was a greater preservation of GSH levels with escalating doses. With all Groups except Group 2, the slopes representing TBARS decreased and by Group 5 there was a greater reduction in TBARS with higher doses (p=0.028). The difference in slopes across all Groups for mitochondrial RATIO was significant (p=0.0012), suggesting an increase in mitochondrial function with higher doses.

**Conclusions:** The high doses of glutamine and antioxidants tested in this dosing study seem to be safe and may have positive effects on some physiological parameters. A larger phase III will be necessary to confirm their therapeutic effects