Research to Practice Activity

"The Best of Times Hokies"

Critically ill patients present with increased reactive oxygen to antioxidant ratio known as oxidative stress. In addition, critically ill patients have been shown to present with decreased plasma concentration of glutamine and antioxidants, which may contribute to the increase in oxidative stress due to a decreased ability to quench reactive oxygen species. Meta-analyses of small-randomized control trials suggest the potential for improved outcomes of critically ill patients when supplemented with glutamine and antioxidants, while studies of a larger scale do not support this effect. The current trial was conducted to assess mortality outcomes of critically ill patients with multi-organ failure when placed on glutamine and antioxidant supplementation upon admission to the ICU. The study's authors hypothesized glutamine and antioxidant supplementation would reduce the 28-day mortality outcomes of these patients.

To determine which patients would be screened for the study, eligible candidates had recently been admitted to the participating hospitals' ICU and placed on mechanical ventilation. Patients were included in the study if the patient presented with two or more organ failures that were directly related to his or her present case of acute illness ($PaO_2/FiO_2 > 300$; hypoperfusion needing vasopressor agents >2hrs; serum creatinine >171 μmol/L/ urine output <500 ml/24 hrs indicating renal disease; platelet count $< 50 \times 10^9$/L). Exclusion criteria included if the patient 1.) Had been admitted to the ICU >24 prior, 2.) Was classified as moribund, 3.) Demonstrated a lack of commitment to aggressive care treatment plan, 4.) Could not receive nutrients enterally, 5.) Presented with a severe brain injury, 6.) Was diagnosed with a seizure disorder and prescribed anticonvulsant medications, 7.) Presented with metastatic cancer or stage IV lymphoma of a life expectancy < 6 months, 8.) Had undergone a routine, elective cardiac surgery, 9.) Presented with burns as the primary reason for admission, 10.) Weighed < 50 kg or > 200 kg, 11.) Was pregnant or lactating, 12.) Was previously randomized in the trial, or 12.) Was currently enrolled in another ICU clinical trial. The exclusion criteria were appropriately extensive for the purpose of this study in order to ensure an equal profile of disease in study participants. A 2 X 2 factorial design was used to randomly assign patients to the four treatment groups. The blinding of the study ensured each patient had equal and unbiased opportunity to receive the treatment. This design was effective to ensure the study was valid, unbiased, and included a control in order to compare outcomes of supplementation. Randomization of patients occurred within 24 hours of ICU admission and patients assigned to the supplementation treatment group received supplementation of glutamine both enterally (30g/day) and intravenously (0.50g/day) in combination with antioxidants selenium (500 μg intravenously and 300 μg enterally), zinc (20 mg enterally), beta carotene (10 mg enterally), vitamin E (500 mg enterally), and vitamin C (1500 mg enterally). One group received only glutamine supplementation, while another received antioxidant supplementation. The study's control group received placebo intravenously and enterally. A P-value of less then 0.044 was considered statistically significant in this trial.

A total of 1218 patients completed the study for final analysis. The supplementation of glutamine alone, when compared with patients who had not received glutamine, was associated with a trend toward increased risk of mortality at 28 days. Glutamine supplementation was also associated with an increased in-hospital mortality and mortality at 6 months. There was not a significant difference in risk for mortality in patients who received antioxidant supplementation alone, and data analysis did not indicate a potential interaction between glutamine and antioxidants in regards to mortality. The lack of a significant effect on mortality in either group receiving antioxidant supplementation challenges the potential therapeutic effect of antioxidants on reduced mortality risk in critically ill patients. The study's authors note that there were 4

potential adverse events in patients that could have been due to the supplemental treatment of glutamine. This may be due to limited prior dosage studies, and a lack of research on outcomes in the severe critical illnesses this study's participants presented with. In the laboratory substudy held in North America at the same time as the clinical trial all baseline plasma glutamine and selenium levels were within normal range at the onset of ICU admission, which contradicts findings of previous studies in which glutamine and selenium levels have been found to be reduced in critically ill patients. These results indicate that initiating glutamine supplementation early in the treatment of critically ill patients presenting with multi-organ failure is potentially harmful, and may lead to an increased risk for mortality in patients.

The study does not present advances in clinical dietetics. The findings provide evidence that further studies need to be done on the effects of glutamine supplementation in order to evaluate the patient population and dosage that would be appropriate to enhance patient outcomes. Until further research is completed, registered dietitians in the clinical setting should not deviate from what is currently recommended regarding glutamine and antioxidant supplementation in their patients.

The Academy's Evidence Analysis Library makes several recommendations in regards to glutamine supplementation in critically ill patients. It is not advised to provide enteral glutamine supplementation, as it has not been shown to improve outcomes in patients. The RD may consider glutamine supplementation via parental nutrition because four or five RCTs have shown this method to reduce complications due to infection in patients. However PN glutamine supplementation did not improve mortality. Therefore, the Academy's Evidence Library concludes that while glutamine supplementation via parental nutrition may improve some outcomes of critically ill patients, evidence does not support a role of glutamine in improved mortality of critically ill patients and enteral glutamine supplementation is not supported in critically ill patients.

1. Heyland D, Muscedere J, Wischmeyer PE, et al. A randomized trial of glutamine and antioxidants in critically ill patients. *The New England journal of medicine.* Apr 18 2013;368(16):1489-1497.