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ANTIOXIDANT AND MICRONUTIRENT SUPPLEMENTATION IN CRITIALLY ILL TRAUMA PATIENTS

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Abstract

Purpose of Review—This paper reviews important nutrients responsible for oxidant-antioxidant balance in critically ill patients requiring admission to the intensive care unit (ICU) and rationale for repletion of antioxidants using pharmaconutrition.

Recent Findings—Oxidative stress is an underlying cause of critical illness due to oxidant-antioxidant imbalance. Multiple nutrients important to oxidative balance have been studied, yet much variety exists among the dosing, timing, and route of administration. Conflict also exists regarding the benefits of particular single nutrients and the effects of combination therapy. Anticipated results of the REDOXS trial hope to provide further insight to the use of antioxidants in critically ill patients.

Summary—The goal of this review, while not exhaustive, serves to highlight recent significant studies regarding antioxidant use in the ICU setting while calling for sufficiently powered randomized, controlled trials to elucidate appropriate guidelines for antioxidant administration in regards to ideal dosing, route of administration, timing of administration, duration of therapy, and the role of single versus combination supplementation.

Keywords

antioxidants; critically ill; intensive care unit; oxidative stress; pharmaconutrition; arginine; glutamine; zinc; selenium; vitamin C; N-acetyl-cystine; fatty acids

Introduction

Severely injured patients requiring admission to the intensive care unit (ICU) suffer from oxidative stress where hypo-perfusion, reperfusion, endothelial injury, and systemic activation of the immune response result in (or worsen) their critical illness.[1] The underlying pathophysiology of oxidative stress is cytokine release and systemic inflammation triggered by reactive oxygen and nitrogen-oxygen species, which leads to mitochondrial dysfunction, tissue injury, organ failure, and death.[1-4]

Antioxidants (AOX) are enzymes such as superoxide dismutase, catalase, and glutathione that catalyze the breakdown of reactive oxygen species. Cofactors required for AOX

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CONFLICT OF INTEREST:
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function include selenium, zinc, manganese, iron, and vitamins C and E.[5, 6] Studies have demonstrated below-normal plasma levels of vitamin C, glutathione, and zinc in severely injured and critically -ill patients.[7] Low levels of selenium are inversely related to the degree of systemic inflammation. Since AOX are depleted after major trauma, sepsis or respiratory failure, their replacement and the restoration of oxidant-antioxidant balance decreases organ dysfunction. Therefore, a decrease in ICU and hospital length of stay (LOS), as well as mortality, seems to be a rational hypothesis and reasonable expectation.[6, 8]

A paradigm shift has occurred transitioning the concept of immunonutrition or immune-enhancing diets to pharmaconutrition where administration of nutrients- including AOX and cofactors- is disease specific and dosed separately from standard nutritional requirements.[4, 9] The shift to pharmaconutrition changes the view of nutrition from adjunctive supportive care to active therapeutic strategy to support cellular defense, decrease oxidative stress, and attenuate the systemic inflammatory response to improve the outcome in severely injured and critically ill patients.[4, 10, 11]

The goal of this review, while by no means exhaustive, serves to highlight recent data regarding AOX use in the trauma setting and outcomes in critically ill patients. While the majority of research has been conducted in non-trauma but critically ill populations, these studies are highly relevant and important to those caring for the seriously injured patients and their findings applicable to trauma patients requiring ICU admission.

Glutamine

Glutamine plays a central role in nitrogen transport, intestinal mucosal integrity, nucleotide and arginine synthesis, and renal angiogenesis.[4, 5] It is the preferred nutrient of enterocytes and is preferentially absorbed over glucose in instances of gut ischemia. Glutamine from muscle acts as a stress signal in sepsis and shock and is important for gene activation to promote cellular protection and immune regulation. Glutamine acts as an AOX by enhancing glutathione levels.[7, 10, 12] In critical illness, glutamine is a conditionally essential nutrient where demand exceeds synthesis or stores from proteolysis. A decrease in supplies of glutamine is associated with immune dysfunction and increased mortality.[4]

Studies have shown that glutamine delivered via the parenteral route has been associated with decreased length of mechanical ventilation, decreased risk of pneumonia, and decreased bacteremia and fungemia incidence.[5, 13] Interestingly, however, these reductions in severity of illness and complications have not consistently been associated with decreased ICU or hospital LOS. Jones and colleagues have demonstrated that glutamine confers a protective effect against insulin resistance, thereby aiding in achieving control in the ICU.[4] The route of administration, however, remains controversial. While equivocal data exists for enteral administration of glutamine, parenteral administration to critically ill patients is a grade A recommendation. In fact, when administered intravenously, glutamine has been noted to aid in prevention and treatment of multi-organ dysfunction syndrome (MODS) after sepsis and critical illness.[13, 14] Weitzel et al advocate for the use of high-dose parenteral glutamine, with doses greater than 0.35 g/kg/day in ICU patients.[11, 14] Finally, pre-operative infusion of glutamine has been shown to reduce muscle cell damage and enhance AOX capacity via elevation of glutathione levels in patients with critical limb ischemia.[15] Glutamine may thereby serve to reduce oxidative stress in patients undergoing lower limb bypass surgery for critical limb ischemia.

Arginine

Arginine is also a conditionally essential nutrient obtained from dietary or endogenous sources via the urea cycle.[5] Arginine serves as a stimulant to release growth factor,

prolactin, and insulin and enhances T-cell function. It plays a role in collagen synthesis and production of somatostatin and glucagon.[4, 6] L-arginine in particular is an important substrate for nitric oxide (NO) production.[5] During oxidative stress, decreased levels of arginine are present as a result of decreased dietary uptake and increased metabolism via NO synthetase to create NO compounds or arginase to create urea and ornithine. Depleted levels of arginine lead to decreased T-cell function and increased risk of infection, making arginine supplementation appear to be a worthwhile adjunct in states of oxidative stress.[4] However, inducible nitric oxide synthetase is up regulated in inflammatory states leading to an increased production of nitric oxide with a potential increased mortality rate associated with arginine supplementation in patients with septic shock.

Gough and colleagues compared 109 severe sepsis patients to 50 control patients, assessing their systemic arginine availability by measuring its ratio to symmetric and asymmetric dimethylarginine (endogenous arginine inhibitors).[16] In this prospective cohort study, a lower ratio of arginine to dimethylarginine was associated with severe sepsis, increased severity of illness and worse clinical outcome. The ratio also independently predicted hospital mortality and risk of death over a six-month time period. The utility of the arginine to dimethylarginine ratio may be useful as a biomarker with potential to augment systemic availability of arginine via supplementation in patients with severe sepsis.

Selenium

Selenium is an essential nutrient that serves as a cofactor for glutathione. A decline in plasma glutathione peroxidase activity correlates directly with decreased plasma selenium levels.[1, 6] Selenium supplementation is thought to improve clinical outcomes in critical illness by decreasing infectious complications and organ dysfunction particularly in septic patients.[13] Forceville and colleagues performed a randomized, double blind, placebo-controlled trial in which the treatment group received high-dose selenium for a ten day course (4000mcg bolus followed by 1000mcg/day infusion for nine days).[17] However, there was no significant difference in vasopressor withdrawal, duration of mechanical ventilation, ICU or hospital LOS or mortality between placebo and treatment groups. Manzanares et al built on this, conducting a study demonstrating that high-dose selenium supplementation (bolus of 2000mcg of selenite followed by 1600 mcg/day continuous infusion for 10 days) provided the dose most likely to restore serum selenium to physiologic levels and safely maximizing glutathione peroxidase activity in critically ill patients.[18, 19] This group of investigators then conducted a prospective, placebo-controlled, randomized, single-blinded phase II study involving 31 patients. The authors noted that such a regimen decreased mean SOFA scores, hospital-acquired pneumonia, and early ventilator-associated pneumonia compared with controls.[20]

Valenta and colleagues conducts a prospective, randomized, single-center clinical trial involving 150 critically ill patients with either SIRS or sepsis and evidence of organ failure or dysfunction.[21] Patients were randomized to receive high dose selenium supplementation (1000mcg of sodium selenite on day one followed by 500mcg daily for a total course of 14 days) or placebo. While this study aimed to prove that high dose selenium would increase plasma selenium levels, decrease severity of disease, reduce markers of inflammation, improve nutritional and antioxidant defenses, and decrease mortality, no significant differences were noted between treatment and placebo groups.

In a multi-center trial from Germany, however, Angstwurm and colleagues found that high-dose sodium-selenite reduced mortality in patients with severe sepsis or septic shock.[22] The investigators randomized 249 patients in 11 German ICUs to receive either placebo or selenium (1000 mcg of sodium-selenite bolus, followed by 14 daily continuous infusions of

1000 mcg). The authors noted that 28-day mortality was significantly reduced in the selenium group (42% compared to 57% in placebo). From a mechanistic standpoint, the investigators demonstrated that selenium concentrations and glutathione peroxidase-3 activity remained normal during selenium treatment, whereas they were significantly decreased in the placebo group.

Zinc

Zinc plays an important role in immune function, glucose control, wound healing, superoxide dismutase and glutathione activity, and thiol pool stabilization.[7, 13] Common clinical manifestations of zinc deficiency include a rash typically seen on the face and gluteal areas, glucose intolerance, abnormal homeostasis, hair loss, altered taste and smell perception, and diarrhea.[23]

Low zinc levels have been linked with immune dysfunction, higher infection rates and increased morbidity and mortality after infection especially in the elderly population and patients with chronic illness. Not surprising, zinc supplementation has also been reported to reduce the duration of pneumonia.[1] Cander et al performed an observational study demonstrating that serum zinc levels are inversely proportional to Sequential Organ Failure Assessment (SOFA) scores and organ failure.[23] Similarly, critical illness, sepsis, and inflammatory states lead to a decline in serum zinc concentrations adding to the belief that zinc supplementation may be beneficial in critical illness. Besecker and colleagues conducted a prospective observational study of 56 medical ICU patients in which plasma zinc levels, cytokine concentrations, and zinc transporter gene expression in peripheral blood monocytes were measured and correlated with illness severity.[24] As zinc levels decreased, all cytokine levels increased significantly (IL-6 and IL-8 showing the strongest correlation). Plasma zinc levels were found to be low in critically ill patients and even lower in the septic patient group. While no studies have demonstrated a significant difference in mortality or difference in length of stay with zinc supplementation, it continues to be included as a part of AOX regimens. Additionally, no data exists reporting optimal dosing or delivery of zinc supplementation.[25]

Vitamin C (ascorbic acid)

Adequate glutathione levels are required to maintain appropriate stores of vitamin C and vitamin E, cofactors important to the oxidant-antioxidant balance.[7] In specific states of increased oxidative stress such as in burns, severe trauma and critical illness, vitamin C may be required in high pharmacologic doses. While it is difficult to quantify deficits, high-dose vitamin C should be considered in patients with oxidative stress. While recommended daily allowances for vitamin C are 90mg for men and 75 mg for women, normal levels of plasma vitamin C levels can be restored with intravenous dosing of 3 g/day of vitamin C in critically ill patients. Parenteral administration is advocated over enteral dosing as a ceiling effect is encountered at 400 mg of daily oral administration.[26] High-dose intravenous vitamin C appears to be beneficial in burn patients and there are no confirmed adverse effects.[27, 28]

Tanaka and colleagues performed a randomized trial in which patients received placebo or high-dose ascorbic acid (66 mg/hr) during the first 24 hours after thermal injury. The investigators noted that the treatment group had significantly lower resuscitation requirements, weight gain, and wound edema. Moreover, the authors noted a decrease in respiratory failure in the treatment arm.

N-acetyl-cystine

N-acetyl-cystine (NAC) serves as an AOX acting directly as a glutathione substitute and indirectly as a precursor for glutathione. NAC causes vasodilatation while inhibiting platelet aggregation, aiding in regeneration of endothelial-derived relaxing factor, and reducing IL-8 and TNF-α production.[1] Controversy exists in the actual utility of NAC in critically ill and injured patients. While some data suggests that NAC may decrease pulmonary morbidity, there is no significant difference in regards to ICU or hospital LOS and long-term mortality.[1, 3, 8] While NAC has been shown to be in reduced amounts in the broncheo-alveloar lavage fluid in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) patients, supplementation has demonstrated no mortality benefit over placebo.[29] In fact, NAC may actually be associated with worsening sepsis and MODS.[1]

Fatty Acids

Fish oils, particularly ω-3 fatty acids, have been shown to suppress excessive endothelial activity, decrease the production of pro-inflammatory mediators, and exert positive effects on pulmonary mechanics.[5] The anti-inflammatory properties of ω-3 fatty acids appear to be related to their ability to displace arachidonic acid from cellular membranes as they compete with ω-6 fatty acids.[4, 6, 29] Current data suggests fish oils may decrease the rate of mortality in ARDS patients with enteral supplementation. However, their impact on overall mortality and ICU and hospital LOS remain controversial.[1, 4, 6]

Animal models have demonstrated that ω-3 fatty acids alter the inflammatory process following states such as hemorrhagic shock through significant reductions in NO synthetase levels and lung edema.[30] Building on this, the Investigating Nutritional Therapy with EPA, GLA and Antioxidants Role in Sepsis Treatment (INTERSEPT) Study Group conducted a prospective, randomized, control study of 106 patients fed a diet of eicosapentaenoic acid, γ–linolenic acid, and AOX versus a control enteral diet.[31] The study demonstrated that treatment patients developed less severe sepsis and/or septic shock compared to those receiving a control diet (26% vs. 50%). In addition, treatment patients developed less cardiovascular and respiratory failure over the control group. While those fed the treatment diet had reduced ICU LOS and overall cost of patient care, there was no effect on 28-day mortality.

Combination Therapy

With glutamine and arginine both being conditionally essential amino acids with interrelated functions, the question remains if combination administration is more advantageous over single nutrient supplementation. While the individual effects of glutamine and arginine are well documented, combination administration can be complex and unpredictable.[32] Since glutamine contributes to *de novo* arginine synthesis, predicting if arginine will preferentially be used for nitric oxide synthesis or polyamines is difficult. Massive supplementation of arginine may have detrimental effects leading to promotion of inflammation, endothelial dysfunction, mucosal swelling, and epithelial damage. Combination of arginine and glutamine may be synergistic or the effects may be inhibitory or neutral.

Nathens and colleagues previously demonstrated that early administration of high-dose antioxidants (vitamin C and E) could reduce infectious complications and organ dysfunction following injury and hemorrhagic shock.[33] Building on this, investigators at Vanderbilt conducted a retrospective cohort study in severely injured patients, using a regimen of vitamin C (1000 mg) and vitamin E (1000 IU) every eight hours, as well as selenium (200 mcg) daily. Their high-dose AOX regimen was associated with a significant reduction in mortality.[34] In a follow-up study, Giladi et al noted that while respiratory failure rates were

significantly lower in the AOX treatment group, there was no difference in renal failure or SIRS.[35] However, the AOX regimen was associated with a significant reduction in infections (surgical site infections, pneumonia, and catheter-related bloodstream infections) and abdominal wall complications (wound dehiscence, surgical site infections, and abdominal compartment syndrome). Moreover, the cost of this seven-day treatment was approximately $11.00 USD per patient.

In 2008, Berger and colleagues reported their findings of a combination regimen administered to post-operative cardiac, major trauma, and subarachnoid hemorrhage patients.[36] Patients were randomized to receive either AOX supplement or placebo for 5 days starting within 24 hours of admission. The AOX and micronutrient supplementation consisted selenium, zinc, vitamin B_1, vitamin C, and α-tocopherol. The investigators noted that in the 66 trauma patients, those receiving AOX supplementation had shorter hospital stays compared with placebo. The study did not demonstrate a difference in mortality between AOX and placebo groups.

A recent meta-analysis of 18 randomized controlled trials examined the impact of AOX on endpoints such as mortality, infections complications, and LOS.[37] In critically ill patients, there exists a potential benefit of micronutrient therapy with a suggested decrease in mortality without significant difference in infections complications. No difference was seen between enteral versus parenteral delivery. Selenium was the most commonly used single nutrient, yet there was great variability in the administration of combination micronutrients as well as dosages among the different studies. Compared to a review in 2005, this meta-analysis found only a small difference in mortality reduction with single nutrient supplementation, while combination micronutrient replacement had a much greater reduction in mortality.[8, 37]

Finally, a recent study from the ARDS-Net investigators noted that combination therapy with fatty acids and AOX did not improve clinical outcomes in patients with acute lung injury and may be harmful.[38] Rice and colleagues carried out a double blind, randomized, multi-center trial of twice daily enteral supplementation of ω-3 fatty acids, linolenic acid, and AOX versus a standard isocaloric enteral feeding. Unlike previous studies, the authors found no difference in ventilator-free days or infectious complications. As well, there was a trend (p=0.11) towards increased adjusted 60-day mortality in the treatment arm. Of note, unlike previous studies supporting fatty acid and AOX supplementation, patients in this study's treatment arm did not have significant reductions in inflammatory mediators compared to the control group. This, and other formulation and dosing differences, may explain the disparity in their findings.

Routes of administration

Advocates of immune-enhancing formulas in high-risk trauma patients recommend the enteral route of nutritional administration over parenteral, with this route being reserved for those patients unable to tolerate enteral feeds.[6] Schneider et al evaluated 58 critically ill patients with SIRS/sepsis in a prospective, single-blinded, randomized fashion in which patients received either low volume enteral supplementation containing AOX/micronutrients (selenium, vitamin E) or diluted standard elemental nutrition.39 The treatment arm feeds were well tolerated and resulted in increased uptake of selenium and vitamin E. Enteral feeds demonstrated improved mucosal integrity and immune function, improved wound healing, and nutritional status. However, no difference was demonstrated over the control group in regards to fever, antibiotic treatment, mechanical ventilation, ICU and hospital LOS, and mortality.

Summary

The role of AOX as pharmaconutrients in severely patients is conceptually appealing in combating oxidative stress with the potential to decrease mortality, reduce LOS, and decrease infections complications. Ideal dosing, route of administration, timing of administration, duration of therapy, and role of single versus combination supplementation still remains unclear. Additional placebo controlled, multi-institutional, randomized controlled studies are needed to answer the above questions. To address this, the Reducing Deaths due to Oxidative Stress (The REDOXS Study) study is finalizing enrollment.[40] REDOXS is examining the impact of high-dose glutamine and/or AOX supplementation on 28-day mortality in 1200 mechanically ventilated, critically ill patients. As well, the group is examining the impact of enteral versus parenteral delivery of these AOX and micronutrients. The hope of the anticipated results of the REDOXS Study is to provide appropriately powered guidelines for the administration of AOX in the ICU.

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HIGHLIGHTS

- Critical illness and injury are associated with severe oxidative stress as a result of cytokine release and systemic inflammation.
- The generation of reactive oxygen and nitrogen-oxygen species leads to mitochondrial dysfunction, tissue injury, organ failure, and death.
- Antioxidants (AOX) catalyze the breakdown of reactive oxygen species or serve as co-factors that facilitate AOX function.
- Low AOX levels have been linked with immune dysfunction, higher infection rates and increased morbidity and mortality during critical illness
- Studies investigating the use of supplementation with single AOX agents, as well as combination therapy or AOX “cocktails,” have been met with mixed results.