

Pilot Study of Antioxidant Supplementation with Alpha-Lipoic Acid and Acetyl-L-Carnitine in Thalassemia and Sickle Cell Anemia.

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Synopsis:

Increased generation of reactive oxygen species (ROS) is integral to the pathophysiology of thalassemia and sickle cell anemia (SCA).^{1, 2} Iron overload from red cell transfusions and increased gastrointestinal absorption produces ROS via the Fenton reaction, which leads to oxidation of biomolecules. Precipitated globin chains, increased superoxide production and recurrent ischemia-reperfusion events damage the red cell membrane and promote hemolysis. While oxidant production is markedly elevated, endogenous antioxidants are depleted in both SCA and thalassemia. Supplementation with compounds possessing broad antioxidant activity could improve endogenous antioxidant stores, alleviate oxidative stress and lead to a significant clinical benefit. Obesity is a state associated with increased inflammation that may be mediated by free radicals. Thus, inflammation in obesity may respond to antioxidant therapy.

We hypothesize that an antioxidant combination of alpha-lipoic acid (LA) and acetyl-L-carnitine (ALCAR) will produce measurable decline in oxidative stress in thalassemia and SCA. We also expect a decrease in inflammation from antioxidant therapy in children with obesity. Prior experimental observations support synergism between these two mitochondrial nutrients in improving oxidative stress and cellular energy metabolism. A successful outcome of the pilot study will facilitate the design of a subsequent clinical trial to evaluate efficacy in reducing the clinical severity of these disorders.

Specifically, we propose to:

Conduct a phase I/II trial of a combination of R- α -lipoic acid and acetyl-L-carnitine in patients with thalassemia and sickle cell anemia, and children with obesity. We will assess:

1. Decrease in oxidative stress by measuring total plasma antioxidant capacity, MDA, protein carbonyls, plasma redox status.
2. Improvement in hemolysis by measuring hemoglobin, reticulocyte count, ektacytometry, phosphatidylserine exposure in subjects with sickle cell disease or thalassemia.
3. Decrease in serum C-reactive protein in children with obesity.
4. Improvement in plasma carnitine level.
5. Adverse effects of LA/ALCAR combination.