REVIEW

DOES VITAMIN E HAVE A ROLE IN TREATMENT AND PREVENTION OF ANEMIA'S?

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ABSTRACT
Vitamin E is a highly effective fat-soluble vitamin with a variety of cellular membrane stabilizing-antioxidant and non-antioxidant functions. Vitamin E has been suggested to prevent the oxidation of polyunsaturated fatty acids in red blood cell (RBC) membrane, thus inhibiting the premature erythrocytelysis. Animal studies have shown that treatment with vitamin E results in increased number of colony forming units of erythroid precursors, enhanced erythropoiesis and improved blood hemoglobin levels in these animals. Several clinical trials have indicated that vitamin E might be used therapeutically as a potential erythropoietic agent for decreasing the premature erythrocyte hemolysis by reducing the fragility of erythrocytes. By this way, it improves the post-supplemental blood hemoglobin and hematocrit levels in some of the anemic human subjects, including low birth weight premature infants, patients suffering from various types of inherited hemolytic anemia, chronic renal failure patients on hemodialysis and apparently healthy mildly anemic subjects.

Keywords: Anemia, antioxidant, vitamin E.

INTRODUCTION

Anemia is a major public health problem worldwide, especially in the developing countries. The highest prevalence of anemia is seen in Africa, but the largest numbers of the anemic individuals are found in countries of South-East Asia, where approximately 315 million individuals have been estimated to be suffering from anemia (Benoist *et al*., 2008).

The causes of anemia are diverse and multifactorial, however, leading etiologies in the developing countries are: nutritional deficiencies, malabsorption, chronic or acute blood loss, inherited genetic defects, chronic diseases, parasitic infestations, premature hemolysis of RBCs, decreased medullary erythropoiesis or an undefined cause (Antonio *et al*., 2009).

Anemia is a not a disease, but rather a sign of an underlying illness. Therefore, management of anemia should focus on identification and removal of the underlying cause. Many of the hematinic micronutrients, including iron, folate, vitamin B_{12}, vitamin B_6, vitamin A, vitamin C and vitamin E have been used in the past for treatment and/or prevention of various types of anemia, with variable hematological responses to these interventions (Fishman *et al*., 2000).

Vitamin E- a highly potent antioxidant

Oxidative stress corresponds to an imbalance between the production of reactive oxygen species (ROS) and the protective capacity of antioxidative enzymes and vitamins, including vitamins A, C and E. Vitamin E was originally considered a dietary factor of animal nutrition, especially important for their normal reproduction. The significance of vitamin E has been subsequently proven as an essentially required cellular component that can protect the integrity of cellular membranes and play an important role in various biological processes.

Vitamin E is an effective lipophilic vitamin, whose major role is to act as a highly potent antioxidant against the damaging ROS and peroxyl free radicals, which are produced as a result of cellular oxidative stress. The main dietary sources of vitamin E include vegetable seeds and their oils, nuts, almonds, fish, some cereals and some of the green leafy vegetables. The term vitamin E refers to eight essential naturally occurring isomeric forms that possess a similar chemical structure comprising a chromanol ring with a 16-carbon side chain. The isomeric forms with saturated side chain are called "tocopherols", while isomeric forms with unsaturated side chain are termed as "tocotrienols" (Muller *et al*., 2010).

The most abundant and biologically active isoform of vitamin E in the human body is alpha-tocopherol (Engin, 2009). Alpha-tocopherol has the maximum bioavailability among all the forms and is selectively recognized and transported inside the cells with the help of a cytosolic liver protein, termed as α-tocopherol transfer protein (Christopher Min, 2007). The most well-known function of vitamin E is to terminate a radical-propagated chain of lipid peroxidation reaction. Vitamin E protects the polyunsaturated fatty acids (PUFAs) of the cellular

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membranes and low-density lipoproteins (LDL) from oxidative damage by free radicals. In this manner, vitamin E serves to protect and stabilize the cellular membranes through its role as a powerful antioxidant (Brigelius-Flohe, 2009).

Non-antioxidant functions of vitamin E

Molecules in biological systems often perform more than one function. In particular, many molecules have the ability to chemically scavenge free radicals, but they may also act as hormones, ligands for transcription factors, modulators of enzymatic activities or as structural components. During the last two decades, the potential impact of vitamin E on health and various life processes has been intensely studied and debated. More recently, vitamin E has been found to possess functions that are independent of its well-defined cellular membrane stabilizing and free-radical scavenging ability (Banks *et al*., 2010).

Vitamin E has been suggested to regulate enzyme activities, signal transduction and gene expression (Sen *et al.,* 2007). It has previously been reported in the literature that the activity of the enzymes such as protein kinase C, tyrosine kinase, 5-lipoxygenase, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and phospholipase A_2 is significantly reduced, while that of diacylglycerol kinase and protein phosphatase 2A is increased in the presence of α-tocopherol (Upadhyay and Misra, 2009). Vitamin E has been shown to modulate the activity of both inflammatory cytokines and immune cells (Huey *et al*., 2008). Vitamin E has also been reported to inhibit smooth muscle cell proliferation (Zou *et al*., 2007). Epidemiological and experimental studies have suggested that antioxidants like vitamin E may play an important role in the prevention of certain chronic diseases. Large scale clinical trials have been carried out to find out the effect of vitamin E supplementation in the prevention of ischemic heart disease, cancers and neurodegenerative diseases (Lee *et al*., 2005; Dong *et al*., 2009; Muller, 2010). However, the results of these clinical studies have been inconclusive, and the expected benefits of vitamin E supplementation in the prevention of some of the chronic diseases need to be clearly shown (Clarke *et al*., 2008; Brigelious-Flohe and Galli, 2010).

Therapeutic uses of vitamin E in prevention and/or treatment of anemia

While iron deficiency is regarded as the major cause of nutritional anemia, insufficient levels of vitamins B_{12}, A, C, E, folate and riboflavin have also been found to be associated with it. Therapeutic use of antioxidant vitamins has gained considerable interest during the last decade (Rodrigo *et al*., 2007). Some of the earlier animal and human studies showed that vitamin E might be having an important role in the prevention of oxidation of PUFAs in RBC membrane, thereby maintaining red cell membrane integrity and inhibiting oxidative stress-induced premature erythrocyte lysis (Elaroussi *et al*., 2007).

Vitamin E has been identified as an essential erythropoietic factor for certain species of animals (Chou *et al*., 1978; Fitch *et al*., 1980). Previous studies have shown that treatment with vitamin E increased the number of colony forming units of erythroid precursors (CFU-E), enhanced erythropoiesis and hemoglobin levels and, thus corrected the experimentally-induced anemia in laboratory animals (Gogu *et al*., 1991; Bartholomew *et al*., 1998; Cherdyntseva *et al*., 2005). However, vitamin E has not been reported to be normally required for erythropoiesis in healthy humans (Drake and Fitch, 1980). Results of some of the clinical trials suggested that vitamin E might be having a role as a potential erythropoietic agent in some of the anemic human subjects, including low birth weight infants, patients suffering from various types of inherited hemolytic anemia, chronic renal failure patients on hemodialysis and mildly anemic apparently healthy subjects.

1. *Results of vitamin E supplementation in premature infants*

Studies have shown that premature infants are born with low serum levels of vitamin E, which may predispose them to enhanced RBC hemolysis by free radicals, including the hydrogen peroxide (Melhorn *et al*., 1971). Treatment of low birth weight infants with routine pharmacological doses of vitamin E has been suggested to control hemolytic anemia, thereby correcting hemoglobin concentration and preventing the development of retinopathy of prematurity and chronic lung disease in these preterm babies (Brion *et al*., 2003).

In a recent study, it was demonstrated that when iron supplementation was given along with dl-alpha tocopherol to 2-3 weeks old preterm neonates, it resulted in significantly increased post-supplemental blood hemoglobin levels along with a decreased reticulocyte count in comparison to the basal levels in these neonates (Arnon *et al*., 2009).

2. *Clinical trials of vitamin E in patients with some types of the inherited hemolytic anemia*

The normal RBC is remarkably pliable, flexible and non-rigid, that is capable of changing its shape as it circulates in the blood stream. Hemolytic anemia is characterized by an abnormal premature RBC lysis, shortened RBC survival time and increased reticulocytosis. Sickle cell anemia, thalassemia, and glucose-6-phosphate dehydrogenase deficiency are all hereditary disorders with greater vulnerability of RBCs to oxidative damage, often resulting in clinical manifestation of mild to severe hemolysis in patients with these disorders. Deficiency of vitamin E is a common feature in many of the hereditary types of hemolytic anemia. Supplementation of vitamin E may have an important role in maintaining red cell

membrane integrity by reducing fragility of erythrocytes and therefore could minimize the severity of some types of the hemolytic anemia. Therapeutic trials had been conducted to determine the role of vitamin E for the prevention and /or treatment for some types of hemolytic anemia.

a. Role of Vitamin E in patients suffering from sickle cell anemia

Sickle cell disease is characterized by formation of a qualitatively abnormal type of hemoglobin, Hb S. Hb S is formed as a result of genetic mutation which causes the substitution of valine for glutamine at the sixth codon of the β-globin chain of adult type of hemoglobin (HbA). With deoxygenation, the Hb S molecule becomes insoluble and polymerizes, so that the intracellular portion of the RBC becomes more viscous. The RBCs then become less flexible, rigid and acquire a sickle shape during passage through the microcirculation. Sickle cell anemia is characterized by increased oxidative stress, which makes the sickle erythrocytes more susceptible to peroxidation in comparison to the normal erythrocytes (Ren *et al*., 2008).

This increased susceptibility to peroxidation had been proposed, in part, due to decreased blood levels of antioxidant vitamins and to an abnormal membrane phospholipid organization induced by sickling. The peroxidative damage of sickled erythrocytes may accelerate loss of cell deformability and a shortened RBC survival (Hasanato, 2006). Decreased plasma levels of vitamin E have been found in patients suffering from sickle cell disease compared to age and body mass index (BMI)-matched healthy controls. Supplementation with alpha-tocopherol in children suffering from sickle cell anemia has been shown to significantly reduce the percentage of irreversibly sickled red cells, increased resistance of RBCs to lysis, increased hematocrit and enhanced blood hemoglobin concentration (Jaja *et al*., 2005).

b. Role of Vitamin E supplementation in thalassemia patients

Thalassemia refers to a group of genetically inherited quantitative hemoglobin disorders, characterized by reduced synthesis of either α or β-globin polypeptide hemoglobin chain and a subsequent imbalance in α/β-globin chain ratio. The relative excess of the remaining non-defective β or α -globin subunit becomes accumulated and precipitated within the red cell precursors, resulting in ineffective erythropoiesis, damage to erythroid precursor membrane and lysis of mature erythrocytes leading to hemolytic anemia. The manifestations of thalassemia range from mild anemia with microcytosis (thalassemia minor/ β-thalassemia trait) to fatal severe anemia (β- thalassemia major). Patients of beta thalassemia major, especially who had a history of multiple blood transfusions, are at a risk of iron overload and enhanced oxidative stress, which may reduce the RBC life span (Athanassios *et al*., 2007). Some of the studies carried out on thalassemia patients have reported significantly low blood levels of antioxidant vitamins including vitamin E in comparison with healthy control subjects (Chiou *et al*., 2006). In order to minimize the oxidative damage to erythrocytes and erythroid precursor cells in thalassemia, intervention trials with antioxidant vitamins, alone or in combination, have been performed.

Some of these trials have shown that supplementation with alpha-tocopherol in patients suffering from homozygous ß-thalassemia was effective in reducing plasma levels of lipid peroxidation end products and a significant improvement in the post-supplemental hemoglobin levels (Das *et al*., 2004). A 4-8 weeks supplementation with vitamin E given to children with various types of thalassemia had been shown to significantly decrease hydrogen peroxide-mediated red cell hemolysis and increase the RBC resistance to oxidative damage (Suthutvoravut, 1993).

c. Role of vitamin E in patients suffering from glucose-6-phosphate-dehydrogenase (G6PD) deficiency

G6PD is a key enzyme in hexose monophosphate pathway, which generates reductive energy in RBC in the form of reduced nicotinamide adenine dinucleotide phosphate (NADPH). NADPH maintains glutathione in the reduced state when erythrocytes are subjected to an oxidative stress. G6PD deficiency is the most common genetic metabolic enzyme defect in human biology. Most common clinical manifestations of G6PD-deficient subjects include neonatal jaundice and chronic hemolytic anemia. In this condition less deformable RBCs are unable to prevent the oxidation of hemoglobin and the red cell membrane. Deficiency of antioxidant vitamins is a common feature in some patients suffering from G6PD deficiency. An acute hemolytic crisis may occur in these patients under certain conditions, such as ingestion of fava beans, certain drugs and severe infections (Abdul-Razzak *et al*., 2008).

Some of the previous reports have indicated decreased blood levels of vitamin E in G6PD deficient patients compared to healthy controls. After 16-week of vitamin E therapy there was significant improvement in blood hemoglobin levels along with decreased reticulocytosis and percentage of hemolysed RBCs in these patients (Eldamhougy *et al*., 1988).

A recent study showed that patients with G6PD deficiency had significantly increased osmotic fragility of erythrocytes compared to healthy controls. After vitamin E supplementation in these patients for 60 days, fragility of erythrocytes significantly decreased, while the blood hemoglobin levels and red cell indices improved towards normal (Sultana *et al*., 2009).

3. *Vitamin E in the treatment of chronic renal failure patients*

Chronic renal failure is characterized by reduced erythropoietin production by the kidney and severe uremia, which may lead to bone marrow suppression, ineffective erythropoiesis, shortened erythrocyte survival and renal anemia. The end-stage renal failure patients usually require long term hemodialysis and renal transplantation. Thus, the need for exogenous erythropoietic factors, including specific hematinic agents is increased in the end-stage renal failure patients.

Recent reports emphasize the role of reactive oxygen species and/or decreased activity of antioxidant systems in chronic renal failure patients, especially those on dialysis (Zwolinska *et al*., 2009).

Several studies have suggested beneficial effects of both oral vitamin E supplementation and vitamin E-coated dialyzer in reducing the hemodialysis-mediated oxidative stress in chronic kidney disease patients (Mydlik *et al*., 2006). During the last decade, recombinant human erythropoietin (rHuEPO) has been used along with some of the antioxidants for treatment of anemia and oxidative stress in these chronic renal failure patients on hemodialysis. As a result of these clinical trials, it has been shown that a combination of rHuEPO and vitamin E therapy for the treatment of renal anemia in chronic renal failure patients on hemodialysis would significantly decrease RBC fragility and increase the post-supplemental hemoglobin and hematocrit levels (Nemeth *et al*., 2000; Cruz *et al*., 2008).

4. Vitamin E in the treatment of apparently healthy subjects with borderline anemia

In a preliminary study, vitamin E supplementation given for a period of 3 months was found to increase the blood hemoglobin levels in mildly anemic adults, with basal borderline levels of hemoglobin (11.6-13.5 g/dl in males and 9.0-10.9 g/dl in females) (Jilani et al., 2008). It was a small study on 30 subjects with mild anemia, however, if the findings of this study could be replicated using a large sample size, it might pave way for a simple and inexpensive way of treating such anemia.

Mechanism of vitamin E in the treatment and/ or prevention of anemia

No definitive mechanism has been reported so far. However, vitamin E might be playing a role in the treatment of anemia by:

a. Inhibiting the oxidation of PUFAs in RBC membrane, thus reducing the fragility of erythrocytes and preventing the oxidative stress-induced premature erythrocyte lysis during various types of hemolytic anemia.
b. Enhancing erythropoiesis in experimental animals and some of the anemic human subjects, thereby, improving blood hemoglobin and hematocrit levels in these individuals.

CONCLUSION

Recent reports have shown that vitamin E has multiple non-antioxidant functions along with its well-established basic cellular antioxidant function. Vitamin E has the potential to be affectively used for preventing/and or treating some types of the human anemia due to its putative role in promoting erythropoiesis, enhancing the integrity and stability of erythrocyte membrane proteins and lipids, and reducing the oxidative stress-induced erythrocyte fragility and lysis. This results in increasing RBC survival and improves blood hemoglobin levels.

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