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Editorial

# Nutritional Supplementation of Donors May Improve Outcomes of Transfusion of Stored Blood

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## Editorial

There continues to be a need for the transfusion of blood products, including red blood cells (RBC), for an array of conditions, such as during and following surgical operations, acute and chronic diseases, traumatic hemorrhagic situations, and in patients receiving chemotherapy for malignancies. Approximately 15 million units of blood are donated yearly in the United States with approximately 32,000 units of whole blood or packed RBC transfused per day. Donated blood may be transfused immediately, but more commonly, the donated units of whole or packed RBC units can be stored for up to 42 days. During storage, alterations in pH and a state of hypoxia can evolve, as well as the formation of toxic substances which can interact with the cell membrane, producing storage lesions [1]. Storage lesions are characterized by both biochemical and biomechanical changes, which can decrease cell viability, including its designed functional capacity following transfusion [2]. The presence and degree of these "storage lesions" and decreasing cell function can potentially increase over the storage period and when transfused has the capacity to affect a patient's acute and long term outcomes. A large (21 studies, 409,066 patients) meta analysis demonstrated that the use of stored blood increased risk of death [3].

Red blood cells depend upon an intact membrane and an internal cytoskeleton to maintain integrity and function. Red blood cells have high levels of 2,3 diphosphoglycerate (DPG) to aid in the delivery of oxygen to our tissue beds. Adequate levels of DPG are important to lower the oxygen affinity for hemoglobin, in which it binds to the beta chain of de-oxyhemoglobin in a pH controlled environment. These RBCs also depend upon an adequate supply of adenosine triphosphate (ATP), to preserve cellular integrity and provide energy for cellular functional. During storage, there is a decline of DPG and ATP levels [4]. Furthermore, an increase in the levels of reactive oxygen species (ROS) from free radical reactions and the formation of advanced glycation end products (AGEs) can produce deleterious changes in RBCs prior to transfusion. Maintenance of membrane structure is paramount for functional stability [5]. The production of AGEs has been associated as a factor in cardiovascular diseases, malignancies, diabetes, etc. Advanced glycation end products may also arise from aldehydes produced by ROS, a likely outcome of storage of RBCs because of the environment that this entails: polyunsaturated fatty acids in close proximity to oxygen and ferrous (redox active) iron. Secondary lipid oxidation products, including aldehydic derivatives of polyunsaturated fatty acids, and cholesterol oxides, have been quantified in human blood lipoproteins [6,7].

Therefore, stored RBCs experience metabolic changes, biomechanical membrane stress, and formation of deleterious ROS. The detrimental role that the three foregoing alterations play can directly affect the function of stored RBCs following transfusion, unfortunately at a time in which optimal function post-transfusion is crucial. Furthermore, damage to the RBCs membrane can produce a negative effect on the recipient's endothelium, potentially creating additional complications following transfusion.

Over the past decade there has been increase awareness and interest in these "storage lesions," as it pertains to cellular viability during storage and the potential clinical complications during and after transfusion of these cells. Furthermore, interest has also centered on potential post-transfusion differences when transfusing RBCs that have been stored for a shorter time period, i.e. "new", versus a longer, i.e. "old", time period. This interest and subsequent investigations have included various types of adult clinical situations, as well as in the pediatric population. A study sponsored by the Cleveland Clinic questioned the status of RBCs that were transfused after a short storage interval of 14 days versus a longer storage time period due to an observed increase in morbidity and mortality in patients undergoing cardiovascular surgery transfused with "old" stored RBCs [8]. Additional publications have observed similar incidences of complications, post-transfusion of "old" stored RBCs in critically ill adult patients, the pediatric population and in trauma situations, in which large volumes of transfused blood are required [9].

The question exists as how to improve the viability and functionality of RBCs that are stored for a longer time period. To our knowledge, all such attempts have focused on post-donation aspects of extending shelf life, including factors such as pH, metabolism, and antioxidants [10]. One reasonably effective method that of anaerobic storage of RBCs, has been published by Yoshida and Shevkoplyas [10]. The reduction in storage lesions and an extension of storage life of RBCs of at least 50% was reported when adding metabolic precursors [10].

Recently, Collard [11] has reviewed the potential role of multiple blood transfusions in the neonate, especially pre-term, low birth weight babies, and the "development of major complications of prematurity." These babies are especially susceptible to oxidative stress and other storage lesions. The contribution of stored packed red blood cells, in particular free redox iron, free heme and free radicals, to the complications of prematurity are discussed [11].

We hypothesize that several potentially fruitful areas could play





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a major role to aid RBCs during their storage period. One aspect would involve the potential to improve the nutritional status and the overall health of the donor prior to the time of donation. For example, donors consuming nutrients and/or nutraceutical supplementation directed at cellular metabolism could potentially offer a benefit. Secondly, cessation of smoking for a period prior to donation, as well as the interplay that specific prescription drugs may have on RBCs, should be studied. The foregoing examples may all impinge upon the formation of "storage lesions," which could potentially benefit the cell's biochemical status and functionality during storage and post-transfusion. Well designed studies directed at the nutritional status and efforts to improve a donor's health prior to donation may help in reducing the development of "storage lesions" and thereby reduce potential complications following transfusion.

The foregoing hypothesis can be easily tested by numerous approaches, some of which could be derived from food technology shelf-life testing. One suggested experiment would entail the collection of blood from donors consuming high vs. low quantities of nutrients. Some obvious nutraceutical choices could include supplemental vitamin E, including both tocopherols and tocotrienols, ascorbic acid, and absorbable carotenoids and flavonoids. Other potential substrates to consider could include ribose and creatine. We believe that examining the development of storage lesions from donors of differing quantities of nutrient intake would provide important fundamental information, not presently at hand. Furthermore, it is tempting to speculate that combining our suggested nutritional approach with the previously reported anaerobic methodology [10] may yield truly significant health benefits to the recipients of donated blood.

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