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Scientific Comment

Red blood cell storage and alloimmunization: a fact or a myth? ☆



Lilian Castilho

Universidade Estadual de Campinas (Unicamp), Campinas, SP, Brazil

Red blood cell (RBC) alloimmunization is a significant clinical complication of transfusion-dependent patients; it is related to delays in obtaining matched blood as well as potentially life-threatening delayed hemolytic transfusion reactions (DHTRs), autoantibody formation, and hyperhemolysis syndrome.¹ Because of its critical significance, the phenomenon of RBC alloimmunization has been investigated in a variety of settings. With a better understanding of the factors that predispose to RBC alloimmunization, it is possible to devise strategies for blood transfusions that reduce the risk of alloimmunization and adverse reactions to transfusion.

Clinical and biological factors such as disease state, human leukocyte antigen (HLA) polymorphisms, underlying inflammation, immunogenicity of the antigens and patient age are independent variables involved in RBC alloimmunization.² In addition, stored leukocyte-reduced RBCs have been reported to produce higher rates of immunogenicity than fresh blood in murine models.³ These findings led to speculate that the transfusion of older RBCs might create a cytokine burst that predisposes a human recipient to RBC alloimmunization and thus raised the interest of some groups to perform studies in humans.

Some recent studies have suggested that RBC storage length is associated with adverse patient outcomes ranging from death to pneumonia to increased length of hospital and intensive care unit stays.^{4,5} RBC alloimmunization was chosen as an outcome in these studies because it can be both medically and logistically problematic.^{6,7} By identifying associations, it may be possible to support or not support changing

in the current inventory management practice of issuing the oldest RBCs first in chronically transfused patients.

Although there are few and limited studies showing the effect of age of RBCs on alloimmunization in humans, some studies did not note any association between the duration of RBC storage and recipient alloimmune responses.^{8,9} However, one recent study in patients with sickle cell disease (SCD) suggested that RBC antibody formation is significantly associated with an older age of RBCs at the time of transfusion but this study has limitations due to its retrospective design in which inflammatory markers were not assessed and because of the small number of patients with new antibody formation.¹⁰ The differentiation of young versus old blood is another variable that influences studies; most often, a storage period of 14 days is used as a cutoff point to define older versus younger blood.

An important retrospective case-control study was performed of a group of alloimmunized patients and non-alloimmunized controls with solid cancer tumors that received non-phenotyped RBC transfusions when the transfusion of older RBC units was investigated as a risk factor for alloimmunization.¹¹ This was the first human study that evaluated the risk of alloimmunization with the transfusion of older RBCs that assured a similar inflammatory background between the study groups. The authors assessed the association between the transfusion of older RBC units (storage time of 14 days) subjected to bedside leukodepletion and alloimmunization in order to confirm previous experimental results and concluded that the transfusion of older RBC units is not a key risk factor for alloimmunization in non-SCD patients. The

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Corresponding author at: Hemocentro, Unicamp, Rua Carlos Chagas 480, Caixa-postal: 6198, Barão Geraldo, 13081-970 Campinas, SP, Brazil.

E-mail address: castilho@unicamp.br

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findings of this study are very interesting and helpful clinically and logistically as they do not reinforce previous experimental data and therefore do not support strategies of providing fresher RBC units as a prophylaxis for alloimmunization.

Some factors known to influence RBC alloimmunization identified in murine models are in the process of being investigated in humans. Although the results obtained by Dinardo et al.¹¹ are in agreement with other retrospective human studies^{8,9} and strongly suggest that the transfusion of older RBC units is not a risk factor for alloimmunization, we should consider that most studies are retrospective and do not compare pre-transfusion samples to post-transfusion samples. Therefore, it is unclear as to whether the presence of an alloantibody is necessarily the result of a previous transfusion. Further controlled prospective studies are probably necessary. Another factor is that the underlying disease-associated immunosuppression in association with chemotherapy may suppress alloantibody production in patients with oncologic disorders.

Conflicts of interest

The author declares no conflicts of interest.

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