

LETTER

Non-leukodepleted red blood cell transfusion in sepsis patients: beyond oxygenation, is there a risk of inflammation?

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Donati and colleagues [1] evaluated the benefits of fresh, leukodepleted (LD) versus non-leukodepleted (nLD) erythrocyte transfusions on the microcirculation in sepsis patients. Oxygenation appeared equal in both groups. Differences between the two kinds of blood cells are presented in Table 1. In the reported study, there is a difference between the age of erythrocytes in the two groups (1.5 to 3 days for nLD versus 3.5 to 5 days for LD erythrocytes; a U test indicates $P < 0.05$); this suffices to influence oxygen delivery mediators (Figure 1). The content of leukocytes prior to (and after) leukodepletion were not tested, nor was the freeing - which is usually very fast - of secreted or docked, soluble biological response modifiers. Considering the dynamics of secreted biological response modifiers in platelet components [2], there must be differences within the two groups, which possibly

influenced sepsis conditions. Residual plasma within erythrocytes given by female donors may include anti-human leukocyte antigen (HLA) antibodies which attack the recipient's lung alveolar epithelium neutrophils, and as sepsis is characterized by the pathology of neutrophils that release microparticles and neutrophil extracellular traps that target lung epithelium [3], it may be feared here that the nLD condition aggravates pulmonary lesions.

The re-evaluation of procedures is infrequent in transfusion despite the rapid evolution of techniques and materials; for example, differential stresses are inflicted on erythrocytes, depending on the collection process (apheresis versus conventional whole blood), with consequences for neutrophils and (vascular) endothelial cells upon transfusion [4]. Clinical investigations and registered trials such as Donati and colleagues are valuable.

Authors' response

Abele Donati, Elisa Damiani, Erica Adrario, Rocco Romano, Paolo Pelaia and Can Ince

We thank Professor Garraud and colleagues for their interest in our study [1]. As underlined, the difference in the age of transfused red blood cells (RBCs) between the nLD group (4 (3.5 to 5) days) and the LD group (3 (1.5 to 3) days) may have influenced the RBC oxygen-delivery capacity. Stored RBCs lose their ability to release vasodilators (nitric oxide, ATP) during hypoxia [5,6]. We showed similar changes in microvascular reactivity (tissue oxygen saturation (StO₂)-upslope) and oxygenation (StO₂) after nLD or LD RBC transfusions [1]. This may indicate that oxygen-delivery mediators were not sufficiently affected to determine relevant variations in the response observed.

Alternatively, heterogeneity in the study population prevented detection of subtle differences. Variability in the response to treatments is common during sepsis. The patient heterogeneity was underlined as a limitation of our investigation [1].

LD RBCs showed a more favorable effect on microcirculatory convective flow [1]. This may depend on the lower adhesiveness of LD RBCs to the endothelium [7]. The transfusion of nLD RBCs decreased blood flow velocity and increased glycocalyx damage markers [1]. Similar effects may reasonably occur in the lungs. As highlighted, anti-HLA antibodies in nLD blood from female donors may contribute to aggravate pulmonary lesions. Nonetheless, the evaluation of respiratory function went beyond our goals.

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Table 1 Possible consequences of variation in transfusion conditions and the type of packed red blood cells administered

Variable	Primary or immediate consequences (efficacy)	Secondary or delayed consequences (hazards)
Total volume	Possibly needs to be adjusted according to the patient's needs	Possibly needs to be adjusted to correct for anemia
Hematocrit	Possibly needs to be adjusted according to the patient's needs	Possibly needs to be adjusted to correct for anemia
Residual plasma volume	Possibly includes anti-HLA antibodies (from female donors) Possibly affects the amount of soluble, free biological response modifiers	Increases the risk of TRALI Increases the risk of inflammation and aggravates the risk of TRALI
Leukocytes	No pre-test (possibly affects donor eligibility) Pre-activation of leukocytes Release of biological response modifiers Release of microparticles and neutrophil extracellular traps HLA antibody targets Infectious risk (intracellular viruses)	Increases the risk of inflammation Aggravates sepsis Increases the risk of TRALI Increases the risk of viral infections
Age of blood	Decreases the benefit of oxygen transport Release of microparticles Expression of stress signals on red blood cells Free iron release NO and iNOS release Oxygenated lipid and lipid degradation	Increases the risk of inflammation Potentiates the risk of TRALI by stressing target neutrophils Possibly increases the risk of allo-immunization

HLA, human leukocyte antigen; iNOS, inducible nitric oxide synthase; NO, nitric oxide; TRALI, transfusion-related acute lung injury.

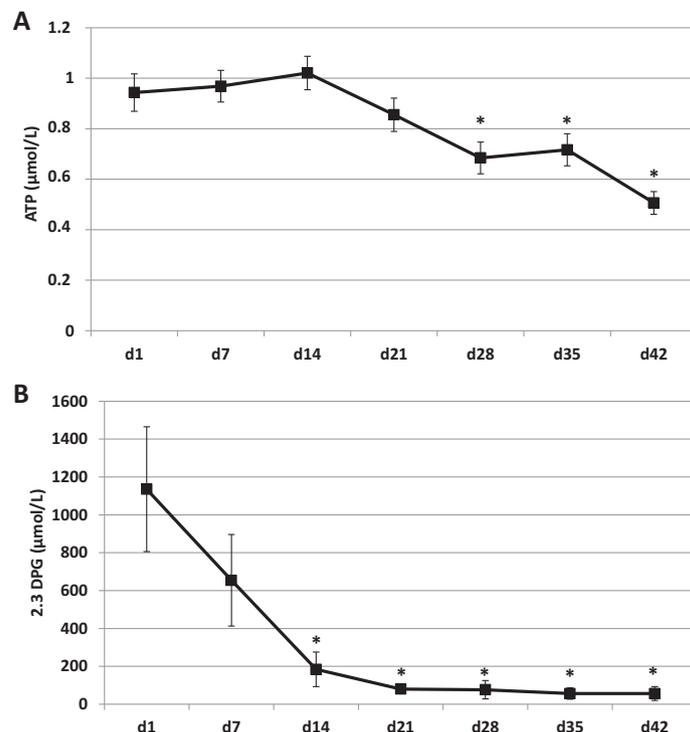


Figure 1 ATP and 2,3-diphosphoglycerate (2,3-DPG) in packed red blood cells. (A) ATP and **(B)** 2,3-DPG in packed red blood cells measured after 1, 7, 14, 21, 28, 35 and 42 days (d) of storage were re-evaluated by one-way analysis of variance. Inter-experiment differences in ATP and 2,3-DPG concentrations at different time points were analyzed by Wilcoxon paired test (XLSTAT® 2010 software, Addinsoft, Paris, France). *P*-values ≤ 0.05 were considered to be significant (**n* = 10). PLT, platelet.

The efficacy of blood transfusion depends on multiple RBC- and patient-related factors. Understanding the response to transfusion during sepsis is a challenging task. Targeting predetermined hemoglobin levels and/or macrohemodynamics is clearly not sufficient. Monitoring the microcirculation may get us closer to the answer [8].

Abbreviations

HLA: Human leukocyte antigen; LD: Leukodepleted; nLD: Non-leukodepleted; RBC: Red blood cell; StO₂: Tissue oxygen saturation.

Competing interests

The authors declare that they have no competing interests.

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