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Impact of Red Blood Cell Transfusion on Platelet Aggregation and Inflammatory Response in Anemic Coronary and Noncoronary Patients

The TRANSFUSION-2 Study (Impact of Transfusion of Red Blood Cell on Platelet Activation and Aggregation Studied With Flow Cytometry Use and Light Transmission Aggregometry)

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Objectives This study sought to determine whether red blood cell (RBC) transfusion increases in vivo platelet aggregation and inflammation in coronary and noncoronary patients.

Background RBC transfusion increases in vitro platelet activation and aggregation in healthy volunteers, providing a possible explanation for the increase in recurrent ischemic events and mortality reported after RBC transfusion in patients with acute coronary syndromes (ACS).

Methods Platelet reactivity was measured before and after RBC transfusion in 61 patients (33 with ACS patients and 28 without ACS). Relative changes between baseline and post-transfusion measurements of maximal and residual platelet aggregation were considered with different agonists as well as changes in vasodilator-stimulated phosphoprotein platelet reactivity index and P-selectin expression. Inflammatory and thrombotic biomarkers were also measured before and after transfusion.

Results After RBC transfusion, platelet reactivity was increased when measured using adenosine diphosphate–induced light transmission aggregometry (11.6% relative increase in maximal platelet aggregation, $p = 0.004$; 10.8% increase in residual platelet aggregation, $p = 0.005$) and vasodilator-stimulated phosphoprotein platelet reactivity index (20.7% relative increase, $p = 0.002$), and there was a nonsignificant trend toward an increase in P-selectin expression. Similar results were found with the nonspecific agonist thrombin receptor–activated peptide (relative increases of 11.7% for maximal platelet aggregation, $p = 0.04$, and 12.7% for residual platelet aggregation, $p = 0.02$) but not with collagen or arachidonic acid agonists. There were no significant differences in inflammatory and thrombotic biomarkers before and after transfusion.

Conclusions After RBC transfusion, there is an increase in platelet reactivity, especially with tests measuring the adenosine diphosphate–$P2Y_{12}$ receptor pathway, without significant variations in inflammatory or thrombotic biomarkers. This in vivo effect may account for the excess of ischemic events observed in the context of patients with ACS treated using percutaneous coronary intervention and $P2Y_{12}$ inhibitors. (J Am Coll Cardiol 2014;63:1289–96)

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Abbreviations and Acronyms

AA = arachidonic acid
ACS = acute coronary syndrome(s)
ADP = adenosine diphosphate
BARC = Bleeding Academic Research Consortium
LTA = light transmission aggregometry
MFI = mean fluorescence intensity
MPA = maximal platelet aggregation
PGE_1 = prostaglandin E_1
PRI = platelet reactivity index
RBC = red blood cell
RPA = residual platelet aggregation
VASP = vasodilator-stimulated phosphoprotein

The recent development of potent antiplatelet therapy has led to a decrease in the rate of recurrent ischemic events and mortality despite a constant increase in major bleeding complications and a more liberal use of allogeneic red blood cell (RBC) transfusion (1–3). Bleeding and/or transfusion have been repeatedly associated with an increased risk for adverse outcomes, including ischemic complications, myocardial infarction, and death (4–6).

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Making the right decisions for patients with acute coronary syndromes (ACS) presenting with anemia and/or major bleeding events remains a clinical challenge. Indeed, the interruption of effective antithrombotic treatment can lead to fatal thrombosis. RBC transfusion represents another challenging issue, with studies suggesting that the conservative use of RBC transfusion is more favorable in hemodynamically stable patients (7–9).

Transfusion by itself has been shown to be an independent risk factor for recurrent ischemic events and mortality (10–12), although the causal link between bleeding or transfusion and mortality has not been fully elucidated yet. We previously demonstrated that in vitro RBC transfusion increases platelet activation and aggregation in healthy volunteers and can potentially contribute to excess risk and a higher rate of recurrent thrombotic event observed in transfused patients with ACS (13).

To further explore the consequences of RBC transfusion on platelet reactivity and inflammatory response, we conducted the Impact of Transfusion of Red Blood Cell on Platelet Activation and Aggregation Studied With Flow Cytometry Use and Light Transmission Aggregometry (TRANSFUSION-2) study to evaluate our primary hypothesis that patients receiving RBC transfusion would exhibit increased platelet reactivity.

Methods

Study population. The TRANSFUSION-2 study is a cross-sectional observational, prospective study conducted by the Allies in Cardiovascular Trials Initiatives and Organized Networks Group at Institut de Cardiologie, Pitié-Salpêtrière University Hospital (Paris, France). Patients with documented coronary artery disease or without coronary artery disease in whom an allogeneic RBC transfusion was prescribed were enrolled in the study. Inclusion criteria were: 1) age >18 years; 2) stable hemodynamic status; and 3) review of and agreement with the study protocol. Antiplatelet therapy with aspirin, clopidogrel, prasugrel, or ticagrelor was allowed. Exclusion criteria were: 1) previous RBC transfusion in the past 7 days; 2) hemodynamic instability with or without a cardiac assist device; 3) glycoprotein IIb/IIIa inhibitor administration within the past 7 days; 4) septic status at the time of transfusion; 5) use of steroidal and nonsteroidal anti-inflammatory drugs; 6) a low platelet count ($<100 \times 10^6$/l); and 7) concomitant transfusion of platelets. Written informed consent was obtained before participation, and this study was approved by the Pitié-Salpêtrière University Hospital Ethics Committee (Comité de Protection des Personnes Participants à la Recherche Biomédicale). The study was conducted and funded by the Allies in Cardiovascular Trials Initiatives and Organized Networks study group (http://www.action-coeur.org) and performed within the Institut National de la Santé et de la Recherche Médicale unit UMRS 937. A research grant was also obtained from Société Française de Cardiologie and Fédération Française de Cardiologie.

Data collection. All clinical and biological data from patients who provided informed consent were collected into a prospective, Web-based registry, as well as drug intake to evaluate drug-drug interactions. ABO type, rhesus group, number of units of recipient blood, and dates of collection and thawing were also obtained for each transfusion pack. Preparation of RBC packs was done according to French legislation (http://www.dondusang.net), and RBCs were obtained at our institution using the classic principle of centrifugation of total blood using saline-adenine-glucose-mannitol as the additive solution, followed and conserved between 2°C and 6°C for a maximum of 42 days.

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