Platelet activation: yet another strike against routine TRANSFUSION

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This editorial refers to ‘Impact of red blood cell transfusion on platelet activation and aggregation in healthy volunteers: results of the TRANSFUSION study’1, by J. Silvain et al. on page 2816

In the past, anaemia in patients with established coronary artery disease, especially acute anaemia as a result of bleeding, has been treated with a relatively liberal use of allogenic red blood cell (RBC) transfusions. RBC transfusions are believed to increase oxygen delivery by increasing haemoglobin concentration. Therefore, transfusion would seem to be a logical approach, as anaemia is associated with a number of maladaptive responses, such as increased sympathetic tone, heart rate, and myocardial contractility, which may all prove detrimental in patients with coronary artery disease.1 Laboratory-based studies further suggest that patients with coronary artery disease may require higher haemoglobin concentrations to maintain oxygen delivery in diseased or occluded arteries.1,2 In one of the largest cohort studies on the salutary effects of blood transfusion, Wu et al. noted that in 78,974 Medicare beneficiaries older than 65 years of age who were hospitalized for acute myocardial infarction (MI), lower admission haematocrit values were associated with increased 30-day mortality, with a rate as high as 35–39% among patients with a haematocrit of ≤27%. RBC transfusion, on the other hand, was associated with a seemingly linear reduction in 30-day mortality for patients who received at least one RBC transfusion if their admitting haematocrit was ≤33%.3 The age-old adage of transfusing for a haemoglobin concentration <10 g/dL or a haematocrit <30% (the so-called ‘10/30 rule’) is still commonly applied.4

More recent studies have suggested a null effect and possibly even an adverse impact of RBC transfusion on cardiovascular outcomes.5 Rao and colleagues examined the potential impact of RBC transfusion in 24,112 patients with acute coronary syndromes (ACS) enrolled in three large international trials. There were significantly higher 30-day all-cause mortality [adjusted hazard ratio (HR) 3.94] and 30-day death or MI (adjusted HR 2.92) rates among patients who received transfusions, as compared with those who did not. Mortality rates were particularly high when transfusions were given to patients with haematocrit values of ≥25% (as compared with those with a haematocrit <25%).6

The management dilemmas arising from acute anaemia due to bleeding, and the pros and cons of blood transfusion, have been encountered with increasing frequency in the last few years with the emergence of several new antithrombotic regimens in patients with ACS. While there has been a significant improvement in reducing recurrent ischaemic episodes, this has been tempered by an increase in bleeding complications.7 Periprocedural bleeding has been shown to be associated with numerous adverse outcomes, including prolonged hospital stay, intraprocedural complications such as coronary perforation, dissection, ventricular fibrillation, and increased risk of MI, stroke, renal failure, and death.8–9 The reasons for the increased morbidity and mortality noted with bleeding are multifactorial. The location (intracranial) or torrential nature of the haemorrhage (gastrointestinal, retroperitoneal) may result in death. Further, patients most likely to bleed are also more likely to have a higher severity of illness such as older age, renal insufficiency, pre-existent anaemia, and presentation with acute MI.10 Antiplatelet therapy such as aspirin and clopidogrel are frequently stopped, which can prove catastrophic in patients with recent percutaneous coronary intervention (PCI). Additionally, cardioprotective medications such as β-blockers may be held.

Thus, while bleeding can have dire consequences, RBC transfusion also seems to be associated with adverse outcomes. The mechanisms behind this are probably numerous and have not been completely delineated yet (Figure 1). General risks associated with transfusion include transfusion-transmissible infections [such as human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV)], haemolytic and non-haemolytic reactions, transfusion-related acute lung injury (TRALI), alloimmunization, citrate toxicity, iron overload, and hypothermia, and are all infrequently encountered.11,12 Prolonged storage of RBCs has also been associated with activation of several inflammatory and prothrombotic pathways. Transfusion, especially of stored blood,
is associated with an increased exposure to plasminogen activator inhibitor (PAI-1). PAI-1 is a soluble procoagulant protein and is an inhibitor of both tissue-type and urokinase-like plasminogen activators that participate in fibrinolysis and wound healing. Experimental models suggest that high PAI-1 levels result in increased microparticle shedding from endothelial cells, as well as a decrease in activated protein C, both of which result in an inflammatory milieu. Shed microparticles also display a high concentration of phosphatidyl-L-serine, which is a potent promoter of factor VIIa generation, and thrombin generation, resulting in an increased tendency to thrombosis. Stored RBCs are also low in 2,3-diphosphoglyceric acid (2,3-DPG). Therefore, the haemoglobin has high oxygen affinity, shifting the oxygen–haemoglobin dissociation curve to the left, and thereby hindering oxygen release to the tissues, with resultant tissue ischaemia. Rheological alterations in the shape of the RBCs with prolonged storage also result in increased fragility and aggregability, resulting in microvascular plugging and tissue ischaemia. Another important effect of blood storage is depletion in nitric oxide (NO) that is carried by RBCs. NO that is produced by vascular endothelium may be bound to RBCs [as S-nitrosothiol (SNO)]. Upon release of oxygen, SNO–haemoglobin may dispense NO bioactivity to microvascular cells, physiologically coupling haemoglobin deoxygenation to vasodilation. NO depletion with prolonged blood storage results in an impaired vasodilatory response to tissue hypoxia, worsening tissue ischaemia. A relative shortage of available NO also promotes platelet aggregation and impairs RBC deformability, compromising flow within the microvasculature.

One of the potential mechanisms independent of duration of blood storage is adenosine diphosphate (ADP) release. In the setting of pre-existing coronary vessel injury, a relatively high level of ADP can provoke platelet-mediated thrombosis or stimulate monocyte and/or neutrophil infiltration of atheromatous plaques—an event associated with plaque instability, rupture, and thrombosis. ADP has also been shown to induce CD40 ligand (CD40L) release from platelets and lymphocytes. CD40L is a soluble transmembrane protein that can bind to endothelial cells and stimulate the expression of metalloproteinases and matrix-degrading enzymes, thus enhancing the inflammatory and prothrombotic milieu. There is also increased interaction between CD40 and CD40L, which contributes to this effect by increasing tissue factor expression on macrophages and reducing fibrinolytic activity.

Silvain and colleagues have now reported the results of the Impact of Transfusion of Red blood cell on platelet Activation and aggregation Studied with Flow cytometry Use and light transmiSSion aggregometry (TRANSFUSION) study. In this elegant ex vivo study, RBCs obtained from transfusion packs were added to fresh whole blood provided by healthy volunteers. Various metrics of platelet aggregation and activation were then performed. The platelet aggregation studies (measured by light
transmittance aggregometry) indicated that both maximal platelet aggregation (MPA) and residual platelet aggregation (RPA) were significantly increased by ADP and collagen post-transfusion, but not by arachidonic acid or epinephrine. The platelet activation studies (measured by flow cytometry) indicated that there was a 2-fold increase in the variation of expression of P-selectin (mediates platelet–endothelium interactions in vivo and is a marker of platelet activation) post-transfusion when activated with ADP. There also seemed to be a small increase in the vasodilatator-stimulated phosphoprotein (VASP) platelet reactivity index (PRI), which has high specificity for the P2Y₁₂ platelet receptor, thus suggesting at least a partial role for this receptor in this pathway.

The study of Silvain et al. thus adds greatly to our knowledge of the potential detrimental effects of blood transfusion. Since these platelet effects appear to be primarily dependent on ADP, it suggests that these effects would be noted independent of the duration of blood storage. Indeed, the authors found no correlation between the length of conservation of transfused blood and increases in platelet activation or aggregation. The current findings may in part also help explain the counterintuitive findings of recent trial data regarding gastrointestinal bleeding, in which continuation of aspirin was associated with lower mortality despite being associated with an increased risk of recurrent bleeding.16 Bleeding can induce platelet activation, as a teleological, protective response. Now, it appears that transfusions can also activate platelets. Thus, in a patient who is actively bleeding and who additionally receives transfusions, marked platelet activation may occur—potentially beyond the degree necessary to stop the bleeding. This may thus predispose to ischaemic events. While the current study pertains to healthy volunteers, the findings may be even more dramatic in patients who have atherothrombosis and some degree of pre-existing platelet activation.

Two limitations of the analysis of Silvain et al. are that this was a small ex vivo study and the subjects were healthy volunteers. Further clinical studies are necessary before these findings can be directly applied to anaemic patients with established coronary disease who receive blood transfusions. This important mechanistic study, however, reinforces the notion that transfusing patients with established coronary disease should only be undertaken when absolutely necessary, and that every effort should be made to continue antiplatelet therapy in these patients while receiving blood transfusions, within the bounds of good clinical judgement and common sense.

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