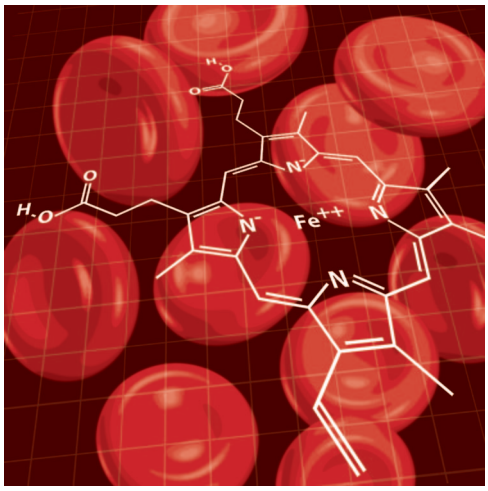
Preoperative Transfusions to Limit the Deleterious Effects of Blood Transfusions

ON a nearly daily basis, anesthesiologists are confronted with the practical dilemma that although anemia increases perioperative risk, transfusion of red blood cells is also associated with increased morbidity and mortality rates. Major complications of blood transfusion include errors in the type and cross-matching process, fluid overload, immunosuppressive effects, and infectious risks. These transfusion-associated problems may be particularly relevant in patients with cardiovascular comorbidities, and thus greater in patients undergoing cardiac surgery than in those undergoing other types of surgery. In cardiac surgical patients, preoperative anemia and perioperative transfusions are both risk factors for renal dysfunction,[1] and anemia and blood transfusion are both associated with worse outcomes.[2] The recent TRACS study,[3] which randomized patients undergoing cardiac surgery to a liberal (target hematocrit 30%) or restrictive (target hematocrit 24%) perioperative transfusion strategy, demonstrated that blood transfusions could be restricted in cardiac surgery without impairing outcomes. In this issue of ANESTHESIOLOGY, Karkouti *et al.*[4] propose an alternative paradigm of prophylactic erythrocyte transfusion as a means of reducing perioperative anemia, adding another dimension to the current debate of how to manage the anemia *versus* transfusion quandary in patients undergoing cardiac surgery.



"Transfusing patients 1 or 2 days before surgery may allow time for iron metabolism to stabilize before the effects of surgery come into play, thus keeping free iron levels at more acceptable, less damaging levels."

In the study by Karkouti *et al.*[4] from their center in Toronto, 60 patients with moderate anemia (hemoglobin concentration 10–12 g/dl) were randomized to receive a blood transfusion 1 to 2 days before cardiac surgery with cardiopulmonary bypass, or to receive intraoperative transfusions as indicated. As expected, patients in the intervention arm became less severely anemic than control patients, and also received fewer blood transfusions. The rationale for the approach proposed by Karkouti *et al.* is that blood transfusions may increase the amount of circulating free iron, which could exacerbate the stress injury during surgery. Free iron catalyzes various oxidative reactions, such as the Haber-Weiss and Fenton reactions, resulting in generation of hydroxyl radicals and oxidative stress, which have been associated with organ damage.[5] Cardiac surgery is associated with damaged erythrocytes in the cardiopulmonary bypass system, which are phagocytosed and the iron extracted by macrophages, resulting in increased iron load. Blood transfusions, especially if the transfused erythrocytes are old and damaged, provide an additional burden for the macrophages, further increasing the iron load. Normally, iron is bound to transferrin in the plasma, but with transferrin levels already decreased after major surgery and iron load increased, the capacity of transferrins to bind iron may be overwhelmed, so that more free iron is available. Moreover, the ability of macrophages to sequester iron is promoted by the hormone hepcidin, the metabolism of which is modified during cardiac surgery so that less hepcidin may be available,[6] thus further increasing iron load. Intriguingly, increased urinary levels of hepcidin are associated with a lower risk of developing renal dysfunction after cardiac surgery.[7] An excellent review of hepcidin's role in iron metabolism has been published recently in ANESTHESIOLOGY.[8]

Transfusing patients 1 or 2 days before surgery may allow time for iron metabolism to stabilize before the effects of surgery come into play, thus keeping free iron levels at more acceptable, less damaging levels. This hypothesis is supported by results from the subgroup of 35 patients in the Karkouti study in whom iron studies were performed: Postoperative

Image: J. P. Rathmell, A. B. Johnson.

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◆ This Editorial View accompanies the following article: Karkouti K, Wijeysundera DN, Yau TM, McCluskey SA, Chan CT, Wong P-Y, Crowther MA, Hozhabri S, Beattie WS: Advance targeted transfusion in anemic cardiac surgical patients for kidney protection: An unblinded randomized pilot clinical trial. ANESTHESIOLOGY 2012; 116:613–21.

transferrin saturation, which may reflect the inability of transferrin to bind enough iron, was significantly increased in patients who received their transfusion later, and increased transferrin saturation levels were associated with more renal dysfunction.

The main endpoint for this study was the efficacy of early transfusion on reducing the severity of perioperative anemia and the need for intra- and postoperative erythrocyte transfusions, and, although measures of acute kidney injury were included, the study was not powered to detect differences in such clinical outcomes. Nevertheless, as discussed by the authors, effects on renal function are an interesting and important target because about one-third of patients develop some degree of renal dysfunction after cardiac surgery.[1] Incidentally, the transfused erythrocytes were relatively old in the present study, averaging about 25 days, and this may have contributed to the untoward effects of transfusions and, thereby, the positive results.

These results are highly interesting and challenging. Some physicians will certainly have concerns about this "preventative" use of blood transfusions. However, it is interesting to note that the total amount of blood transfused was not significantly greater in patients who received a preoperative transfusion. This study is not really about whether to give more or fewer transfusions – if you need a transfusion, you will receive it sooner or later – but about the timing of transfusion. So, should we be giving more preoperative blood transfusions before cardiac surgery? Maybe it is a little early to start such a discussion; this study was only a single center, pilot trial, and the potential benefit of the proposed protocol remains a hypothesis. Nevertheless, these results add to the mounting evidence that altered iron metabolism may contribute to organ dysfunction after major surgery. We look forward to reading more about this important issue.

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