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(Accepted for publication November 3, 2009.)

The Evidence Shows That Allogeneic Transfusion Is Associated with Reduced Survival after Coronary Artery Bypass Surgery

To the Editor:

Beginning with the 2002 landmark publication by Engoren *et al.* on the effect of transfusion on survival after cardiac surgery, multiple investigators have shown an association between transfusion and adverse events including short- and long-term mortality.[1–7] All these studies included larger numbers of patients than in the study by Weightman *et al.* in ANESTHESIOLOGY. This large body of studies is remarkably consistent in the finding that transfusion in a dose-dependent manner confers an increased risk of short- and long-term mortality in cardiac surgery. Contrary to these earlier findings, the recent study by Weightman *et al.*[8] concludes by stating "Patients who have undergone coronary artery surgery and who have received moderate amounts of blood . . . should be reassured that they are unlikely to experience a reduction in long-term survival." This statement reaches far beyond what the data in their study show.

How should we interpret the findings of Weightman *et al.* in the context of the previously published evidence? In a variety of well-designed, although nonrandomized, studies, tallying more than 30,000 cardiac surgery patients, there is a consistent "hazard signal" regarding the effect of erythrocyte transfusion on short- and long-term outcomes in cardiac surgery. None of the previously published evidence suggests that erythrocyte transfusion is either safe or effective therapy for anemia in patients undergoing cardiothoracic surgery. One possible explanation offered by the author is that previous studies failed to include preoperative anemia as a mortality risk factor in their analysis. Preoperative anemia is a marker for transfusion; it may also independently predict reduced long-term survival in patients with coronary artery disease.[9] However, it is highly unlikely that decreased short- and long-term survival in transfused cardiothoracic surgery patients simply reflect the risk of preexisting anemia.

Examination of the data of Weightman *et al.* suggests a number of serious limitations. The data are stratified into four groups based on the number of units transfused: no transfusion, 1–2 units, 3–6 units, and >6 units. Stratification severely dilutes the conclusions and leads to a type II error. Furthermore, the 95% confidence limits for the point estimates for the groups receiving 1–2 units or 3–6 units are very wide and only powered to exclude hazard rates greater than 40%; the possibility of a hazard rate less than 40% may have been falsely rejected. This is a significant limitation to this study given the size of earlier studies and should limit the breadth of any conclusions. As Weightman *et al.* state, this study was inadequately powered.

Plasma, platelet, and cryoprecipitate units transfused were included in the data in equal weight to erythrocyte transfusions. This confounds the analysis and is different from any previous study. It is unlikely that the short-term or any long-term consequences of platelet transfusion, and especially transfusion of acellular blood components such as plasma and cryoprecipitate, will be identical to that of erythrocytes. These products should not have been included in the analysis.

The authors state that "There were 250 subjects who died during follow-up who did not have a history of malignant disease at the time of surgery, comprising 77 subjects in group 1 and 183 in the transfused groups." Because this total is 260 rather than 250, one or both of these numbers is incorrect. (The total number of deaths stated elsewhere in the article is 266. The number of deaths occurring in patients who reported a history of malignancy before surgery and subsequently died during the follow-up is stated to be 16, leaving 250 deaths in patients without a history of malignancy, not 260).

Finally, there is the influence of new malignant conditions on the cumulative hazard of mortality by (the) transfu-

sion group. A new cancer-related diagnosis after surgery was not included in the model, yet there was a disproportionate number of subjects who died with a cancer-related diagnosis in the group not receiving transfusion compared with the transfused groups ($P = 0.03$). If subjects who died from a cancer-related diagnosis are excluded from the analysis, mortality data from the three transfusion groups pooled, and the cumulative mortality rate recalculated to compare patients who received any transfusion with those who were not transfused, the mortality rate for transfused patients is more than twice that of patients who were not transfused (13.2% *vs.* 6.0%). This is a striking finding consistent with previous studies.

What should we tell our patients and how should we approach the transfusion decision in the setting of cardiothoracic surgery? First, as we demonstrated, the data presented in this study do not provide reassurance that patients who receive perioperative transfusion are unlikely to experience a reduction in long-term survival; this remains an open question, with current evidence favoring a restrictive transfusion strategy being associated with lower mortality. At a minimum, there seems to be no benefit to transfusion in the majority of patients. Transfusion is associated with substantial cost[10] and a host of well-documented risks, including disease transmission, hemolytic reactions, acute lung injury, and circulatory overload. Therefore, strategies to optimize hemoglobin and minimize bleeding and transfusion should be used.

Transfusion rates of greater than 50% in uncomplicated coronary artery bypass procedures should no longer be tolerated. A number of programs have demonstrated the ability to perform coronary artery bypass surgery with transfusion rates consistently less than 20%.[11] Transfusion in cardiac surgery should be an uncommon event. More data are needed, but until then, the decision to transfuse should continue to be viewed as one that carries substantial risk but no proven benefit in the hemodynamically stable patient.

The authors thank the Society for the Advancement of Blood Management, Milwaukee, Wisconsin.

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(Accepted for publication November 20, 2009.)

Blood Transfusion and Survival in Cardiac Surgery

To the Editor:

It is postulated that blood transfusion has been associated with cancer promotion because of the adverse effect of blood transfusion on the immune system. In contrast to a number of cited studies, Weightman *et al.* found no association between transfusion of up to six units of blood and long-term survival in cardiac surgery patients.[1] They attributed this discrepancy, at least in part, to their multivariate analysis that included anemia as a risk factor.

Because cardiopulmonary bypass (CPB) causes a state of temporary immunodeficiency, it has been suggested that CPB negatively affects the host defense against malignancy. Platell[2] found that the cancer-specific survival rates of patients with colon cancer were reduced after surgery with CPB. Thus, as an alternative explanation for their discrepancy, I hypothesize two related possibilities that will need to be tested. Perhaps, the incremental adverse effect of blood transfusion on the immune system in patients who have been on CPB is not enough to make a measurable effect on tumor promotion and long-term outcome until a sufficiently large number of packed erythrocytes have been transfused. Sec-