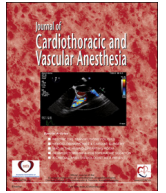




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## Editorial

## Blood Transfusions in Cardiac Surgery: Balancing Science and Art



WHAT IS the impact of blood transfusions on clinical outcomes in cardiac surgery? Given the relatively high transfusion rate in cardiac surgery, it is worth pondering this question in more detail. For in-hospital or short-term post-operative outcomes there is plenty of evidence from high-quality randomized clinical trials (RCTs) in cardiac surgical patients that giving a certain amount of blood is good, but giving excess blood provides no benefit or can even be harmful.<sup>1–4</sup> However, what remains to be determined is whether transfusions have any impact on longer-term outcomes, at 1 or more years following cardiac surgery. Reasons for concern include reports from retrospective, observational studies of immune suppression from allogeneic transfusion, with a possible predisposition to infections<sup>5–7</sup> or cancer.<sup>8,9</sup> To date, only one large prospective RCT has reported long-term outcomes and no adverse effects related to transfusion were apparent.<sup>10</sup>

Virtually all retrospective studies show worse outcomes with transfusion, most often with a dose-dependent association between transfusion and adverse outcomes. The problem, however, is the substantial degree of confounding in retrospective studies, since transfusion is tightly linked to both severity of illness and complexity of the procedure.<sup>11</sup> For this reason, virtually all retrospective studies reporting both short- and long-term outcomes, show worse outcomes in transfused patients. Because of this severe confounding associated with retrospective transfusion studies, and the abundance of high-quality prospective RCTs, most retrospective studies have only little impact on clinical practice. In this issue of the journal, however, Tantawy et al.<sup>12</sup> report an important retrospective study in patients undergoing cardiac surgery, using methods that carefully adjust for confounders and results that include both short-term and long-term outcomes. The long-term outcomes are perhaps most interesting, given the relative uncertainty of the effect(s) of transfusion on long-term outcomes.

Tantawy et al. looked at patients undergoing coronary artery bypass (CAB) surgery at a single institution over an 8-year

time period using data submitted to the Society for Thoracic Surgery (STS) registry. Using a one-to-one propensity score matching, they derived 2 groups of patients with surprisingly similar characteristics—although about 50% of patients were excluded in the matching process. This difficulty to match the groups is most likely explained by the dissimilarity between transfused and non-transfused patients and when not accounted for, can be a major source of confounding. The 2 groups they choose to evaluate were those receiving no red blood cell (RBC) transfusion, and those receiving 1-5 RBC units during the hospitalization. Patients receiving 6 or more units were excluded from the study. Mortality rates at 1, 3, and 6 months were considered short-term outcomes, and mortality rates at 1, 2, 3, and 4 years long-term outcomes. Overall the authors report no significant mortality difference at 6 of these 7 time points, with the only difference being a higher mortality at 3 years after surgery in the transfused group (11% v 6.7%;  $p = 0.038$ ). At 4 years, however, the difference in mortality was not statistically significant for the transfused (11.9%) and non-transfused (8.3%) groups;  $p = 0.079$ . The conclusion the authors draw from this is that perioperative RBC transfusion, after careful risk-adjustment, was not associated with increased short- or long-term mortality.

The strengths in Tantawy's study include the primary outcome they chose—mortality, which is neither subtle nor subjective. In addition, this may be one of the few retrospective studies that take rigorous enough precautions against confounding, as evidenced by the extremely similar baseline characteristics in their matched transfused and non-transfused groups. Weaknesses include the exclusion of about half their patients as a result of propensity matching, missing data on the cause of mortality, no outcome assessments other than mortality, and the lack of a post-hoc statistical adjustment for multiple comparisons or adjustment of the level of significance. If the authors were to employ the commonly used Bonferroni adjustment, a  $p$  value of 0.0071 would have been needed to demonstrate a significant difference for any of the 7 time points for which mortality was compared between groups. Even though the authors did not use such an adjustment, they appropriately concluded that their study

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was negative for between group differences, since the difference at the end of the 4-year period was not significant. Lastly, mortality, while certainly being impactful, is not the only important clinical outcome, and morbidity, reinterventions, or functional status would have been interesting to include.

But why would we expect transfusion to have long-term consequences at all? Much of the literature evaluating long-term outcomes after transfusion focuses on cancer recurrence after tumor resection. One major contributing factor linking cancer recurrence and transfusion is transfusion-related immune modulation (TRIM), which is thought to occur by way of complex immunological effects of allogeneic transfusion involving microchimerisms,<sup>13</sup> however the degree and clinical relevance of immune suppression after transfusion remains controversial. Nonetheless, observational studies<sup>9</sup> and a meta-analysis on colorectal cancer surgery<sup>8</sup> have shown increased cancer recurrence in transfused patients. After risk adjustment, however, the impact of transfusion is either diminished or absent.<sup>9</sup> However, while immune function is similarly important for patients after cardiac surgery, to the best of our knowledge, TRIM after cardiac surgery has not been studied extensively.

Consequences of transfusions after cardiac surgery have been studied though. In an observational study Koch et al.<sup>14</sup> examined long-term outcome up to 10 years following CAB surgery comparing transfused with non-transfused patients. As expected in this and virtually all other observational studies, the transfused patients were sicker and underwent more complex surgeries. Nonetheless, there was an increased mortality, which was dose-related for transfusion, remained significant after risk adjustment, and was present to 10 years after cardiac surgery. This finding was not surprising given that previous studies have shown transfusion to be an indicator for increased longer-term mortality in population-based studies and after cardiac surgery. Engoren et al.<sup>15</sup> showed that after CAB surgery, transfused patients had twice the 5-year mortality compared with non-transfused patients, an effect that remained after risk adjustment. In our opinion, however, transfusion may be so inextricably linked to severity of illness and complexity of the procedure that routinely used statistical analyses for risk adjustment may not adequately separate the effect of transfusion from other unaccounted risk factors for adverse outcome. The findings of Tantawy et al. showing no long-term consequences, compared with these older studies that did show long-term effects, may therefore be explained by the stringent statistical methods using a well-constructed propensity score for matching patients. It is likely that multivariable analyses by itself are not adequate for risk adjustment in observational transfusion studies, and a careful propensity matching might be more appropriate. This is in concordance with the similarity of the findings by Tawtawy et al. and the only RCT to date showing data on long-term follow up—the FOCUS trial, which did not show a transfusion-related increase in mortality out to 5 years.<sup>10</sup>

In this context, the high quality RCTs done comparing liberal with restrictive transfusion strategies in cardiac surgery certainly need to be recognized. These are rigorous, difficult to conduct studies, which require large amounts of external funding. In fact, there are now 4 such studies in cardiac surgery dating back to Bracey in 1999,<sup>1</sup> Hajaar in 2010,<sup>2</sup>

Murphy in 2015,<sup>3</sup> and most recently the largest RCT ever regarding transfusion, with almost 5,000 patients by Mazer in 2017<sup>4</sup>—the TRICS III study. Importantly none of these trials showed a difference in the primary outcome with a restrictive hemoglobin trigger (7.5–8 g/dL) compared with a liberal hemoglobin trigger (9–10 g/dL). One study (Murphy et al.)<sup>3</sup> showed a single worse outcome with a restrictive strategy, but only for one secondary outcome (90-day mortality) with a *p* value of 0.045, which would not have been statistically significant if they had done a post-hoc test adjusting for multiple comparisons. Perhaps the most interesting and noteworthy finding in the TRICS III study was in the subgroup of elderly patients (with age  $\geq 75$  years), which was the median age of their CAB patients. With just over 2,400 of these elderly patients, they found the primary adverse outcome to be increased with liberal transfusion.<sup>4</sup> In our opinion this seriously questions the commonly held notion that has never been demonstrated in any other well-designed study, namely that older patients should be transfused liberally to a higher hemoglobin level—just because of their age.

In conclusion, the observational study published in this issue of the journal by Tantawy et al. is an important addition to the transfusion literature despite the inherent limitations of such studies. After careful adjustment for confounders, the results show that allogeneic blood transfusion does not impact long-term outcomes out to 4 years following cardiac surgery, consistent with the rigorous RCTs for short-term outcomes, and the 1 RCT that examined long-term outcomes. The most concise, summary we can make for this study and the numerous other studies on transfusion-related outcomes is that “blood saves lives when you need it, but only increases risks and costs when you don’t.” The challenge is to correctly identify this need and it is our job as perioperative caregivers to determine who needs blood and who does not, which sometimes is just as much of an art as it is science.

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