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Journal Club

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Association of donor age and sex with survival of patients receiving transfusions. Edgren G, Ullum H, Rostgaard K, et al. *JAMA Intern Med*. 2017;177:854-860.

There has been increased focus on factors that can affect packed red blood cell unit (PRBC) quality. For example, a number of randomized controlled trials have suggested that older stored blood does not lead to worse outcomes. Another interesting area of research is related to the effect unit donor age and sex has on transfused patients. Two recent observational studies reached opposite conclusions with one showing no effect and the other showing worse survival with PRBCs from young or female donors. To explore this contradiction, the authors of the first study repeated an analysis of their data using the methods of the second study. The results show how differences in statistical methods can significantly affect results.

Edgren et al used the SCANDAT2 database that includes data on blood donations and transfused patients in Sweden and Denmark. They included patients transfused at least 1 PRBC between 2003 and 2012. The main outcome was death both 30 days posttransfusion and long term. The authors used 3 statistical models to control for the association of death with number of transfusions received: log-linear, categorization into groups (eg, 1-10, 11-20 transfusions), and fitting into a restricted cubic spline. The authors also used 2 models for multivariable analysis. One method included all variables in the same model, whereas the other separated out the donor age and sex characteristics (ie, 7 analyses for each 10-year age group block, 1 analysis for male donors and 1 analysis for female donors).

Of the 1 015 159 patients in the database, 981 971 received at least 1 PRBC. There were 13 271 patients excluded because of uncertain donor identity or autologous transfusions, for a final number of 968 264 patients. The median age of patients was 73 years with 57% women. Patients received a mean of 3.7 transfusions. In regard to donors, the most common donor age for transfused units was between 40 and 49 years, with numbers decreasing as donor age increased or decreased. There were more units transfused from male donors.

Of the different models for controlling for donor age, the cubic spline had the best fit. When looking at survival, the unadjusted and log-linear models showed worse outcomes for the oldest (>70 years) and youngest (<20 years) donors and for female donors. When controlling for number of transfusions using categorization or the spline model, this association disappeared. In addition, use of the single multivariable model or multiple model analysis showed similar results (ie, the log-linear model showed an association, whereas the spline model did not).

Most impressively demonstrating how the statistical method affects results, the authors took their unit data and randomly "transfused" different patients in the cohort. Even in this scenario, older and younger age donors were significantly linked with worse survival using the unadjusted and log-linear models, with the association disappearing using the spline model.

Edgren et al provide a useful statistical lesson. Controlling for number of transfusions and disease severity is critical in analysis of transfusion outcomes. If not done adequately, transfusion will appear to cause harm. In this case, sicker patients less likely to survive were more likely to receive multiple transfusions. When someone received multiple transfusions, they were more likely to be from rarer donor groups (ie, older, younger, or female donors), leading to confounding of donor age and sex with worse outcomes. (RH)

Transfusion requirement in burn care evaluation (TRIBE). A multicenter randomized prospective trial of blood transfusion in major burn injury. Palmieri TL, Holmes JH, Arnoldo B, et al. *Annals of Surg* 2017; epub ahead of print.

Although it is clear from numerous clinical trials for the average hospitalized patient, a threshold for considering transfusion in the absence of hemorrhage or symptoms is 7.0 g/dL. Whether this threshold is optimal for all hospitalized patients is unclear because it has not been studied in every patient type. Here is just a study that fills one of these knowledge gaps—up until now, we had no data regarding the safety of the 7.0 g/dL threshold in patients with major burn injury. As a result, studies have shown widely disparate transfusion practices by the physicians caring for these patients. This is the TRIBE study. The primary objective was the impact of the transfusion threshold on blood stream infections (early threshold studies had suggested a difference in rates, but this has not been shown to be true in systematic reviews and meta-analyses of subsequent trials). The secondary objectives were mortality, number of infections, length of intensive care stay, hospital length of stay, and numerous others. Despite the liberal group receiving 1906 more units of red cells, there was no observable improvement in any measured outcome.

Overall, 347 patients at 18 centers in the United States, Canada, and New Zealand were randomized to a threshold of either 10 or 7 g/dL. They were required to have at least a 20% surface area burn or greater with anticipated need for burn excision or grafting. Children 18 years of younger, pregnant patients, and those with chronic anemia were excluded. Importantly, patients experiencing angina or with acute myocardial infarction were excluded. Patients were stratified by age and burn size to ensure 2 equivalent study groups in each arm. Red cell transfusions were given one at a time with a hemoglobin repeat before more units were administered. The exception to this rule was

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transfusions given for hemodynamic instability in the operating room where the pretransfusion hemoglobin was not required before emergency transfusions. Compliance with the protocol was high in both arms (91% in the liberal group and 88% in the restrictive group), and virtually all episodes of noncompliance were during episodes of bleeding or hemodynamic instability.

There was a large difference in the median number of red cells transfused per patient (7 vs 15 U in the restrictive vs liberal groups, respectively; $P < .001$). In terms of the primary outcome, incidence of blood stream infections, there was no difference (24% in both arms). There were no differences in any of the secondary outcomes, mortality included. Subgroup analyses of patients with and without a history of cardiovascular diseases were not reported. The authors estimate that if a restrictive transfusion strategy was adopted across the United States, the cost savings would be in the order of US $31 to 47 million per annum.

These authors are to be commended for the conduction of this trial to allow for widespread adoption of a restrictive strategy in patients with burn injuries. There were no data reported on the number of adverse reactions to transfusion. Given that an extra 1906 U of blood was administered, one would expect dozens of extra reactions reported in the liberal arm. Perhaps, the authors are holding these data back for a subsequent publication. The data are getting clearer and clearer that very few nonbleeding patient groups need transfusion thresholds above 7.0 g/dL. We just need to push the Choosing Wisely agenda harder to convince more physicians to choose wisely. (JC)

Safety and cost efficiency of a restrictive transfusion protocol in patients with traumatic brain injury. Ngwenya LB, Suen CG, Tarapore PE, et al. *J Neurosurg* 2017; epub ahead of print.

We all accept the evolving evidence base to promote restrictive use of red cell transfusions. However, these data are largely based on patients enrolled into trials set in general critical care or surgery. Significant subgroups of patients may be missing from these trial datasets. One of these is traumatic brain injury (TBI). Because of the contrasting and unique concerns about brain hypoxia in association with anemia in these patients, many clinicians are reluctant to translate the findings supporting restrictive thresholds for hemoglobin concentrations to drive red cell transfusion need, and we know this from our audit data.

This retrospective study reports on a large analysis of patients with TBI, aimed to provide follow-up data on safety and cost-savings. At a Level I trauma center, the researchers compared patients with TBI who were managed with a restrictive (target hemoglobin concentration >7 g/dL) vs a liberal (target hemoglobin concentration >10 g/dL) transfusion protocol. The data set included patients with TBI admitted to the intensive care unit (ICU) between January 2011 and September 2015. Patients <16 years of age and those who died within 24 hours of admission were excluded. Demographic data and injury characteristics were then compared between groups, and multivariable regression analyses were used to assess hospital outcome measures and mortality rates. Estimates from an activity-based cost analysis model were used to present changes in cost alongside the implementation of a restrictive transfusion protocol.

A total of 1565 patients with TBI who were admitted to the ICU were included in the study. Modeling analyses were reported to show that a restrictive transfusion strategy was associated with fewer days of fever, defined as >38.5°C ($P = .01$), and that patients who received a transfusion had a larger fever burden. ICU length of stay, ventilator days, incidence of lung injury, thromboembolic events, and mortality rates were not significantly different between transfusion protocol groups. A restrictive transfusion protocol also appeared to save approximately $115 000 annually in hospital direct and indirect costs.

On the plus side, this is a large study to report outcomes with restrictive transfusion protocols in patients with TBI. The results suggest that a unit-wide change to a restrictive transfusion protocol appears safe and cost-effective in patients with TBI. Are the data enough in this one study to support a broader change in practice? My answer would be no. There are pitfalls associated with this design of study, and for example, there were some differences in baseline characteristics. What is much harder for me to address, if I was a "funder," is how to justify the need for specific large trials of red cell transfusions in *all* "problematic" patient subgroups such as cardiac disease, bone marrow failure, or TBI, where we feel that there are real limitations to generalize from the clinical settings of surgery and critical care (and this is the trial data as incorporated into very recent systematic reviews). (SJS)

Randomized trial of red cell washing for the prevention of transfusion-associated organ injury in cardiac surgery. Wozniak MJ, Sullo N, Qureshi S, et al. *Brit J of Anaesth* 2017;118:689-698.

Many transfusion medicine technologists, clinicians, and scientists think that washed red cells are safer for patients. You can probably understand the natural bias in favor of washed red cells—it sounds cleaner! This is the REDWASH trial—a multicenter, randomized, single-blinded trial of washed compared with standard red cells in patients undergoing cardiac surgery at high risk for large volume transfusion. The trial was planned for 170 patients, but because of slow recruitment, the trial was terminated early; this report includes 60 randomized subjects with a planned laboratory substudy. With the limitations of the small numbers of patients included, there was no apparent benefit of washing in terms of biomarkers in the products/patients or clinical outcomes. This trial makes a case for restriction of washed red cells for patients with clear indications or only in the setting of a clinical trial.

This trial included adult, high-risk cardiac surgery patients at 3 centers in the United Kingdom. Randomization was stratified by site and type of surgery; this resulted in 2 balanced groups with the exception of more renal dysfunction in the washed arm. Washed cells were provided intraoperatively and for 48 hours postoperatively. The washing was performed at the bedside with the Continuous AutoTransfusion System (CATS; Fresenius AG, Germany), and the unit was immediately transfused. The primary outcome was the serum interleukin-8 (IL-8) at baseline and 4 postoperative measures. They also measured markers for red cell microparticles, platelet activation, leukocyte activation, cell free hemoglobin, non–transferrin-bound iron, troponin, endothelial microparticles, and endothelial activation at baseline, 6 hours, 12 hours, 24 hours, and 48 hours. Their trial was challenged by protocol violations in the washed arm with 6 of 29 patients in the washed arm receiving unwashed red cells.

Patients in the washed arm needed more red cells (3 vs 4 U, $P = .04$), which is not surprising because there is red cell loss during washing. There was no difference in the primary outcome (IL-8 levels). In addition, there were no differences in any of the biomarkers assessed in patient samples or clinical outcomes. Washing reduced the number of red cell microparticles, but this did not translate into lower red cell microparticles in the recipient (the authors hypothesized that the bypass circuit induced microparticles overwhelmed any beneficial effect of washing). Washing actually doubled the amount of cell free hemoglobin in the red cells.

The authors found that washing was logistically challenging and failed to alter either clinically significant outcomes or biomarkers of inflammation and cellular activation. Their study is limited by the small sample size but should make "believers" of washing be more skeptical about the benefits of this intervention. For the rest of us "nonbelievers," we will need to see adequately powered clinical trials before we consider routine washing of red cells for surgical patients. (JC)