



Article Appraisal

Article: Restrictive or liberal red-cell transfusion for cardiac surgery. New England Journal of Medicine 2017.

Date of Journal Club: January 16, 2018

Resident Reviewer Name(s) and Residency Affiliation: Dr. Elizabeth Pursell (FRCP-EM PGY-2)

Faculty Methodology/Bio-statistics Resource Person: Dr. Rob Stenstrom

Background and Study Objective(s):

Patients undergoing cardiac surgery often have decreased cardiovascular reserve and may be exposed to hemodilution during surgery; however, the safe threshold for transfusing blood in cardiac surgery patients is not well established. Multiple observational studies provide evidence that transfusion is linked with increased morbidity and mortality, suggesting that a restrictive strategy might be of greater benefit. However, the TITRe2 study in 2016 aroused concern about this practice as it suggests that in post-operative cardiac surgery patients, the restrictive transfusion strategy was associated with greater morbidity and mortality. The aim of the TRICS trial was to determine if a restrictive transfusion strategy was non-inferior to a liberal transfusion strategy in the peri-operative period among moderate-to-high risk patients undergoing cardiac surgery.

Study Design:

This was a randomized controlled non-inferiority trial that took place across 73 sites in 19 countries, including Canada, and VGH and KGH specifically. It included patients >18 years of age who were scheduled to undergo cardiac surgery with cardiopulmonary bypass who had a moderate-to-high risk of death as per the EuroScore I of 6 or greater (corresponding to an in-hospital mortality risk of >4%). Patients were randomized to either the liberal (received blood if Hgb <9.5 g/dL intra-operatively or in the ICU, or <8.5 g/dL on the ward) or restrictive (received blood if Hgb <7.5 g/dL intra- or post-operatively) transfusion strategy. The primary outcome was a composite outcome of death, non-fatal MI, stroke, or new-onset renal failure requiring dialysis. The secondary outcomes included blood product transfusion, lengths of stay, and various clinical events.

Results:

This study showed non-inferiority of the restrictive transfusion strategy in this population of patients compared to a liberal transfusion strategy with a power of 90% to detect a margin of inferiority of 3%. As this is a non-inferiority trial, the results focused on the per-protocol analysis. As would be expected, more patients in the liberal transfusion group (72.6%) received a blood transfusion than the restrictive transfusion group (52.3%) and patients in the liberal group overall received more blood (median of 3 units, compared to 2 units in the liberal vs. restrictive groups, respectively). There was no significant difference between the primary composite outcome, which occurred in 12.5% of patients in the liberal group, compared to 11.4% of patients in the restrictive group. There were also no significant

differences in the individual components of the primary composite outcome or any of the secondary outcomes between the 2 strategies. These results were consistent in the modified intention-to-treat analysis. A sub-group analysis was also conducted and the only difference found was in patients aged >75, in which the restrictive strategy was associated with a lower risk of the primary composite outcome (Odds ratio 0.70).

Validity of Results:

Overall, this was a well done study with strong internal validity. Interestingly, initially the study authors chose a sample size to provide a power of 85% to detect non-inferiority with a margin of 3%. The sample size was increased mid-way through the study in order to increase the power to 90%. It is unknown why the authors did not just start with a power of 90%, as is custom in non-inferiority trials.

One of the limitations of the study was that the patients and health care providers were unable to be blinded; however, the outcome adjudicators were blinded. Additionally, the patients were enrolled using a variable-sized block randomization strategy to minimize the effect of enrolment bias. The secondary outcomes considered were extensive; however, one of the criticisms from the discussion in Journal Club was that the authors did not include “transfusion reactions,” which seemed like an oversight when assessing the safety of transfusion strategies. Additionally, the patients that were assigned to the restrictive transfusion strategy had an average post-operative Hgb concentration 1g/dL less than those assigned to the liberal transfusion strategy. This may have diminished the ability of the study to detect differences in safety outcomes as it results in dilution of the difference in the number of patients receiving blood and the amount of blood these patients received.

The authors reported both the per-protocol (allowing for 90% or greater adherence to protocol) and modified intention-to-treat analyses: the results of were consistent between these analytic strategies although it was discussed whether only 90% adherence may have been too liberal and may have diluted the true effect.

Generalizability of Results:

This study not only included Canadian hospitals, but VGH and KGH specifically. Therefore, this study is applicable to this particular population of patients in our centres. However, peri-operative cardiac surgery patients is not a population that is representative of the patients that present to the Emergency Department. Therefore, this has very minimal generalizability to the Emergency Department patient population.

The Bottom Line:

A restrictive transfusion strategy is non-inferior to a liberal transfusion strategy in moderate-to-high risk peri-operative cardiac surgery patients. Despite the liberal transfusion strategy cohort receiving more blood overall, there were no statistically significant differences in mortality or various indicators of morbidity between these interventions.

Overall, this study lends some support to consider using a more restrictive transfusion strategy in patients with cardiac disease, but by no means provides strong evidence or is practice changing in the Emergency Department.