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Lessons from the trials

Transfusion Indication Threshold Reduction (TITRe2) trial: When to transfuse and what to give?

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INTRODUCTION

Anemia is a common association with cardiac surgery that has been repeatedly proven to increase morbidity and mortality.[1] This anemia is classically treated with blood transfusion, which has also been linked to mortality and its own set of morbidities, in addition to an increase in health service costs leading to the general adoption of a restrictive policy for blood transfusion in the western world.[2,3] With randomized controlled trails failing to prove any difference between liberal and restrictive transfusion thresholds,[4] a cut-off for initiating transfusion remains to be found. In an attempt to answer this clinical question in the unique cardiac surgical cohort, the TITRe2 (Transfusion Indication Threshold Reduction) investigators carried out a randomized controlled trial, the results of which were published in the *New England Journal of Medicine* last March.[5]

TITRE2 TRIAL

The trial was conducted at 17 centers in the United Kingdom. Patients above 16 years, undergoing non-emergency cardiac surgery were enrolled. Excluded from the trial were patients who would not receive blood or blood products, patients with diseases in the blood or coagulation system, and those with sepsis or critical limb ischemia. During the post-operative period patients whose hemoglobin fell below 9 mg/dL or hematocrit below 27% were divided into two groups; liberal (transfusion threshold below 9 mg/dL) and restrictive (transfusion threshold below 7.5 mg/dL). From July 2009 to February 2013, 2,003 participants were randomized equally between the two groups.

The *primary end-point* was a composite of any serious infectious or ischemic event in the first three months after randomization. With infectious events being defined as sepsis or wound infection and ischemic event as stroke, myocardial infraction, gut infarction or acute kidney injury. The *secondary end-points* were: a- number of units transfused, b- intensive care unit (ICU) stay and hospital stay, c- pulmonary complications, d- the occurrence of either an infectious or ischemic event in isolation, and e- all-cause mortality. The patients were followed during their hospital stay and three months after randomization by telephone or mail.

There was no difference in the primary end-point; observed in 35.1% of the restrictive group and 33% of the liberal group (odds ratio, 1.11; 95% CI, 0.91 to 1.34; $p = 0.30$) or any of its individual parts. 53.4% of the restrictive group and 92.2% of the liberal group received blood transfusion with the former receiving a median of one unit and latter two units with no difference in the use of other blood products. There was also no statistically significant difference in the ICU or hospital stay or the occurrence of pulmonary complications. Hospital and health-care costs were similar between the groups. The only end-point which reached statistical significance was 30-day mortality: 2.6% in the restrictive group and 1.9% in the liberal group and 90-day mortality: 4.2% and 2.6% respectively ($p = 0.045$).

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DISCUSSION

The investigators concluded that the restrictive threshold was not superior to the liberal threshold with respect to post-operative morbidity or total costs. A restrictive strategy may be better by virtue of using fewer units, thus avoiding transfusion reactions, acute lung injury and infectious disease transmission, although the higher risk of death in the study remains an unexplained concern. It is of importance to cardiac patients that exposure to human leucocytic antigen in blood cells may sensitize to future heart transplant. This conclusion was consistent with other randomized controlled trials where there was no difference between transfusion thresholds.[4]

The study showed, on the other hand, liberal transfusion to have the advantage of lower mortality and a trend towards better freedom from acute kidney injury. A proposed explanation may be that cardiac patients have less reserve and therefore cannot withstand anemia, thus confirming a similar study looking at transfusion practices in patients with coronary artery disease.[6] Their trend towards more renal complications with the restrictive strategy was more evident when a quarter of the patients who had received packed red blood cells before randomization were removed from the cohort. These results were contrary to a number of observational analyses showing increased risk of morbidity and mortality with liberal transfusion.[7]

The recruitment of patients from 17 centers had the advantage of recruiting a large number of patients, but that may come at the expense of diverse practices in blood conservation, such as; the use of medications such as alpha-aminocaprioc acid and aprotinine, surgical sealants, and coagulation factors. In addition there could be differences in cardio-pulmonary bypass priming volume and use of mini-bypass circuits. The authors also report non-adherence to treatment in both study groups reaching 25%. Non-adherence was defined as either the failure to transfuse red cells within 24 hours after a patient's hemoglobin fell below threshold, or transfusion when the hemoglobin was above threshold. That raises a question of whether patients who received blood before their hemoglobin dropped were considered sicker and vice versa and has that significant deviation from study protocol had an impact on the observed difference in mortality?

To tackle a different, but perhaps equally important, angle a recent study by Jobes et al. looked at type of transfusion used. They retrospectively studied over 4,000 patients younger than 2 years who underwent elective cardiac surgery with the use of fresh whole blood as the type of blood transfusion and compared them with previously published studies.[8] Whole blood was drawn from on-site emergency donors and transfused within 48 hours from donation. They found a substantial improvement in hemostasis with the use of fresh blood, more so when the fresh blood was used to prime the cardio-pulmonary bypass circuit. The need for additional transfusions was halved (median of 1 unit of fresh whole blood versus median of 2 units of packed red blood cells) and the number of donor exposures was significantly reduced. This reduction in number of transfusions required would, in turn, decrease the risk of transfusion related morbidity.

WHAT HAVE WE LEARNED?

Cardiac surgical practice heavily utilizes transfusion of blood and products. In the United States, trauma and cardiac surgery account for nearly 40% of all blood products transfused.[9] In other specialties, where minimal or no blood transfusion is required, one would assume that transfusion per se indicates that the procedure was complicated, or the patient was sicker which would explain a higher incidence of morbidity and mortality.

Not all cardiac surgical patients are the same and risk stratification; according to factors such as age, renal status and body mass index, may be required to tailor transfusion thresholds. A study by Ad et al.[10] focused on old age as a predictor of blood transfusion after cardiac surgery found that within a protocol driven post operative transfusion practice older patients are more likely to require blood transfusions which were also associated with longer post-operative length of stay and poorer survival.

Despite the commendable efforts of the investigators, the question of *when* to give blood transfusion in cardiac surgery was not answered. With each strategy having its pros and cons further study is needed with more subgrouping. Transfusion of fresh blood in a timely fashion could aid in achieving hemostasis and reducing blood requirements. It might be the answer for the question of *what* to give. This theory remains to be tested with a randomized controlled trial.

As the search continues, the decision for transfusion of blood or blood products will continue to be an exercise of clinical judgment where factors like patient age, comorbidities and type of operation

come into play. Reduction of transfusion requirements will remain a practice that starts before the operation, with good patient preparation, and is consequence of sound surgical technique, rather than a substitute.

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