Transfusion Medicine Reviews 31 (2017) 230–235

Contents lists available at ScienceDirect

Transfusion Medicine Reviews

journal homepage: www.tmreviews.com

Evidence-Based Red Blood Cell Transfusion Practices in Cardiac Surgery

Nishith N. Patel [a,*], Gavin J. Murphy [b]

[a] National Heart & Lung Institute, Imperial College London, Hammersmith Campus, London, UK
[b] Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester, UK

ARTICLE INFO

Available online 21 June 2017

Keywords:
Review
Red blood cell transfusion
Observational study
Clinical trial
Cardiac surgery

ABSTRACT

Cardiac surgical patients are among the highest consumers of allogeneic red blood cells (RBCs) due to the prevalence of anemia and bleeding. Up until recently, there was a paucity of high-quality evidence informing transfusion decisions in this patient group which led to wide variability in transfusion decision making. The article reviews and critically analyzes the available evidence for RBC transfusion in cardiac surgery, focusing on trials of transfusion triggers and age of blood, and provides suggestions for future research. Observational studies analyzing outcomes in patients transfused vs those not transfused have consistently shown RBC transfusion to be associated with adverse outcomes. However, multiple sources of bias in these studies invalidate their conclusions. The best available evidence comes from randomized controlled trials which compare liberal vs restrictive transfusion thresholds. To date, 6 randomized controlled trials have been reported in cardiac surgical patients, and pooled analyses have shown no differences in clinical outcomes between the 2 strategies. Similarly, research into age of RBCs and adverse outcomes has failed to demonstrate a pathological effect attributable to the storage lesion; the recent multicenter Red Cell Storage Duration Study (RECESS) trial has demonstrated no difference in outcomes between patients receiving fresh or old RBCs. Future research needs to identify what a safe transfusion threshold may be, and how this differs for different patient groups and different stages of the perioperative journey. There is also a need to evaluate other physiological parameters which, coupled with hemoglobin concentration, can better inform those patients who need an RBC transfusion.

Contents

More than 440 000 patients receive red blood cell (RBC) transfusions per year in the United Kingdom [1]. More than 20 000 of these patients are cardiac surgical patients. Therefore, cardiac surgery consumes 5% of all RBC units in the United Kingdom [1]. The rationale for perioperative RBC transfusion in cardiac surgery is to improve or preserve oxygen delivery in the setting of blood loss and anemia. The decision as to when transfusion is indicated is complicated by several factors; severe anemia and excessive blood loss are common in this setting, patients with cardiovascular disease are considered to have different transfusion requirements to other patient groups [2], and much of the existing high-quality evidence to guide this decision is derived from studies in noncardiac surgical patients. Moreover, the existing data, whether in patients with cardiovascular disease or without, are unclear as to the risks or benefits of transfusion. Whereas observational studies have shown strong associations between RBC transfusion and outcomes such as death, stroke, renal failure, or sepsis, contemporary randomized controlled trials (RCTs) in a range of clinical settings have failed to

* Corresponding author at: Nishith Patel, PhD, FRCS (C-Th), NIHR Academic Clinical Lecturer, National Heart and Lung Institute, Imperial College London, Hammersmith Hospital Campus, Du Cane Rd, London, W12 0NN, UK.
E-mail address: Nishith.patel@imperial.ac.uk (N.N. Patel).

http://dx.doi.org/10.1016/j.tmrv.2017.06.001
0887-7963/

demonstrate a causal relationship between transfusion and these outcomes [3-6]. Observational studies showing associations between transfusion and adverse outcomes suffer from numerous systematic biases that can confound these analyses, as patients receiving RBC transfusion tend to be sicker and have a greater disease burden. In contrast, RCTs are typically undertaken in low-risk selected cohorts that may not be representative of clinical practice. As a consequence, uncertainty as to the appropriate indications for transfusion persists, and this is reflected in variable clinical practice with transfusion rates ranging from 8% to 93% between cardiac surgical units in contemporary cross-sectional studies [7,8]. The aim of this review is to critically analyze the available evidence for RBC transfusion in cardiac surgery, focusing on trials of transfusion triggers and age of blood, so as to better inform clinical decision making and future research.

Consequences of Anemia in Cardiac Surgery

Observational studies in adult cardiac surgical patients have demonstrated that preoperative anemia and/or nadir hematocrit during cardiopulmonary bypass (CPB) are independently associated with postoperative mortality and morbidity [9-18]. For example, patients with preoperative anemia have a 2- to 3-fold increased risk of developing postoperative acute kidney injury. Similarly, nadir hematocrit during cardiopulmonary bypass of less than 21% is associated with worse outcomes. Perioperative RBC transfusion is an important confounder when evaluating the association of anemia with postoperative outcomes. Several studies have assessed outcomes in patients undergoing cardiac surgery with CPB but who did not receive any RBC transfusion. They found that both preoperative anemia and nadir hematocrit on CPB were independent risk factors for postoperative morbidity [9,11,16]. These studies suggest that the treatment of preoperative anemia and the reversal or avoidance of perioperative anemia should reduce adverse outcomes following cardiac surgery. The current standard of care for these patients typically involves a multimodal strategy including iron treatment, red cell transfusion, surgical diligence, use of hemostatic adjuncts, and reversal of coagulopathy [19].

Risks of RBC Transfusion in Cardiac Surgery

The risks of infection and hemolytic reactions arising from transfusion errors are rare [20]. However, observational studies demonstrate associations between RBC transfusion and mortality and organ injury [21]. Specifically, RBC transfusion in cardiac surgical patients is associated with increased short- and long-term mortality, acute lung injury, acute kidney injury, stroke, myocardial infarction, sepsis, surgical site infections, and increased use of health care resources with prolonged intensive care unit and hospital stays [22-24].

Large observational cohort studies have several strengths; they compare large groups of patients and evaluate objective clinically important end points, often using robust follow-up data. For example, it is common for observational studies to report outcomes in many thousands of patients by linking databases of routinely collected administrative data to national mortality and morbidity databases [13,22,24-26]. They demonstrate a dose-response relationship (Fig 1); that is, increasing units of RBC transfusion are associated with greater adverse outcomes [26], a feature that should increase the likelihood of causality [27]. However, as discussed below, this relationship is actually attributable to the worsening clinical state of the patient rather than implying causality.

Observational cohort studies typically compare transfused with nontransfused patients. This is an apparent strength to the uncritical mind, but herein lies the greatest weakness of these studies which invalidates their conclusions. The comparison transfusion vs no transfusion is not a clinically relevant question; it would not be ethically justified to consider no transfusion as a treatment policy because the risk of death and other serious adverse events is extremely high in patients with severe bleeding or anemia: transfusion can be lifesaving, and no alternatives to transfusion in such patients are available. However, observational studies compared transfusion with no transfusion. It follows that estimated effects of transfusion from observational studies are likely to have been subject to unmeasured confounding because they included in the transfusion group patients who became so severely ill during surgery that they could never have remained transfusion free. The Transfusion Requirements After Cardiac Surgery (TRACS) and Transfusion Indication Threshold Reduction (TITRe2) trial investigators clearly demonstrated the potential for such bias by presenting their results according to their randomized intention-to-treat analyses (ie, liberal vs restrictive transfusion) and then, as a secondary analyses, comparing patients who did and did not receive an RBC transfusion in their trial population, as per an observational cohort analysis. The intention-to-treat comparison in both trials showed no evidence of an adverse effect of a liberal transfusion strategy [6,28]. However, the secondary multivariable logistic regression analyses of the data from both trials comparing patients who did and did not receive an RBC transfusion found that RBC transfusion was strongly associated with a higher risk of mortality. Moreover, transfused patients were older and had higher Euroscores, longer CPB times, higher lactate values at the end of the operation, higher Acute Physiology and Chronic Health Evaluation II and Simplified Acute Physiology Score II scores, and longer intensive care unit and hospital stay compared with those who were not transfused. Even after adjusting for these factors, receipt of transfusion was independently associated with an increase in adverse outcome. This apparent adverse effect increased with greater transfusion volume. These results indicate that the association between transfusion and adverse outcome is not causal but is an indicator of sicker patients requiring transfusion, or confounding by indication.

Observational studies also suffer from lead-time bias. For example, observational studies determine outcomes in patients from the time of exposure to the intervention, that is, transfusion, and not the point of clinical decision-making, that is, severe perioperative anemia. This produces a lead-time bias that falsely exaggerates the pooled effect estimate by excluding clinical adverse events in patients that may have been severely anemic but were not initially transfused.

Another problem of focusing on RBC transfusions is that they are often associated with variable amounts of coagulation factor transfusion that is not included in the analysis. When patients bleed, in addition to RBCs, they often require additional factors including platelets, plasma, cryoprecipitate, and other potential factor concentrates that contribute to outcomes. Transfusion of non–red cell components is likely to confound observational analyses. This is one of a large number of likely confounders associated with this type of study. Others include anemia and bleeding. Despite use of complex statistical methods, such as propensity score matching and multivariate regression, it is extremely difficult to measure and control for all the factors influencing the decision to transfuse because these vary during the operation and may be impossible to measure at times of emergency intervention. This leads us to question whether the results of existing observational studies should inform clinical decision-making.

Trials of Liberal vs Restrictive Transfusion in Cardiac Surgery

To date, 6 RCTs recruiting 3352 cardiac surgical patients have been published [6,28-32]. All cardiac surgical RCTs compared restrictive with liberal RBC transfusion strategies. Five used transfusion thresholds based on perioperative hemoglobin or hematocrit values, whereas 1 used a threshold based on red cell volume. Transfusion thresholds varied between 7.0 and 8.0 g/dL in the restrictive arms and between 8.0 and 10 g/dL in the liberal arms. Four RCTs included only low-risk surgical patients undergoing elective cardiac or coronary surgery and thus excluded patients at the highest risk of requiring RBC transfusion—those undergoing emergency or redo surgery, who had preoperative anemia or organ dysfunction, impaired left ventricular function, or postoperative massive bleeding. Only 2 RCTs included high-risk patients