A Randomized Clinical Trial of Red Blood Cell Transfusion Triggers in Cardiac Surgery

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Background. Class I evidence supporting a threshold for transfusion in the cardiac surgical setting is scarce. We randomly allocated patients to a transfusion hematocrit trigger of 24% versus 28% to compare morbidity, mortality, and resource use.

Methods. From March 2007 to August 2014, two centers randomly assigned 722 adults undergoing coronary artery bypass graft surgery or valve procedures to a 24% hematocrit trigger (n = 363, low group) or 28% trigger (n = 354, high group). One unit of red blood cells was transfused if the hematocrit fell below the designated threshold. The primary endpoint was a composite of postoperative morbidities and mortality. Treatment effect was primarily assessed using an average relative effect odds ratio, low versus high, 0.86, 95% confidence interval: 0.29 to 2.54, p = 0.71). However, the low group received fewer red blood cell transfusions than the high group (54% versus 75%, p < 0.001), mostly administered in the operating room (low group, 112 [31%]; high group, 208 [59%]), followed by intensive care unit (low, 105 [31%]; high, 115 [34%]) and floor (low, 41 [12%]; high, 42 [13%]). The low group was exposed to lower hematocrits: median before transfusion, 22% (Q1 = 21%, Q3 = 23%) versus 24% (Q1 = 22%, Q3 = 25%).

Conclusions. Negative exposures differed between treatment groups, with lower hematocrit in the 24% trigger group and more red blood cells used in the 28% group, but adverse outcomes did not differ. Because red blood cell use was less with a 24% trigger without adverse effects, our randomized trial results support aggressive blood conservation efforts in cardiac surgery.

on cardiopulmonary bypass (CPB [Supplemental Fig E1]), to avoid enrolling patients unlikely to reach either trigger.

**Context**

The trial enrolled adults aged 18 years and older scheduled for elective isolated heart valve procedures, coronary artery bypass graft surgery (CABG) with or without valve procedures, and ascending aorta replacement performed on CPB at two centers: Cleveland Clinic (USA) and SAL Hospital (India).

The trial was approved by the Institutional Review Boards of each center and was registered at clinicaltrials.gov (#NCT00651573). Screening and consenting of patients were by research personnel from the Department of Cardiothoracic Anesthesiology, without surgeon involvement. Therefore, surgeons were blinded to the study arm, as were personnel assessing patient outcomes and the patients themselves. However, clinical care for actively bleeding patients superseded the trial protocol.

**Randomization and Intervention**

Consenting patients meeting inclusion criteria were randomly assigned at time of surgery to a hematocrit trigger of either 24% or 28% for the duration of hospitalization. Randomization was stratified by site, using within each site randomly sized blocks of 6, 8, 10, and 12 so that at any given time, approximately equal numbers of patients were randomized into each transfusion trigger group. A single unit of RBC was transfused when the hematocrit fell below the assigned trigger. Other management decisions were left to the care team.

Our prior work demonstrated that nadir hematocrit commonly occurred just after initiation of CPB [12]. Therefore, the transfusion target was allowed to vary by ±2% from the assigned threshold during CPB because a degree of hemodilution was deemed desirable.

**Endpoints**

A multidisciplinary Data and Safety Monitoring Board adjudicated clinical events. The primary endpoint was a composite of inhospital postoperative morbidity and mortality, as defined for the Society of Thoracic Surgeons National Cardiac Database: (1) inhospital mortality or multisystem organ failure; (2) neurologic morbidity (stroke or coma); (3) pulmonary morbidity (pneumonia, pulmonary embolus, or prolonged postoperative ventilation >24 hours).

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Fig 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram. (HCT = hematocrit.)

![Consolidated Standards of Reporting Trials (CONSORT) flow diagram.](image)
hours); (4) renal failure; (5) infectious morbidity (deep sternal wound infection or sepsis); (6) cardiac arrhythmia (atrial fibrillation or ventricular tachycardia, fibrillation); (7) asystole; (8) gastrointestinal morbidity; (9) reoperation (for bleeding/tamponade, graft occlusion, valve dysfunction); and (10) vascular morbidity (aortic or femoral artery dissection or acute limb ischemia). Vascular morbidities were excluded from the composite in the primary analyses because their frequency was low.

The first 200 SAL Hospital patients were not assessed for sepsis or acute limb ischemia; analyses assumed that these patients did not have those low-frequency complications. Sensitivity analyses—randomly imputing sepsis and acute limb ischemia outcomes based on each outcome’s occurrence in the remaining SAL Hospital population—did not change any conclusion.

Secondary endpoints were lengths of ICU and postoperative hospital stays, number of RBC units transfused, and individual components of the composite. Although the Short Form (SF)-12 was scheduled to be administered at 1 and 3 months postoperatively, logistics precluded this, and a single SF-12 was administered between 1 and 3 months postoperatively.

Sample Size
Sample size was based on the primary composite endpoint and an estimated event occurrence of 25.7% for the 24% hematocrit trigger and 34.2% for the 28% trigger [13], a type I error of 5%, and power of 90%, all of which yielded 632 patients per arm. To account for interim looks at 25%, 50%, and 75% of trial enrollment and to account for monitoring both efficacy and futility [14, 15], a sample size of 668 patients per treatment arm was required (Appendix E1).

Statistical Analyses
Study design and analyses utilized SAS version 9.3 (SAS Institute, Cary, NC), R statistical software version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria), and East version 6.3 (Cytel, Cambridge, MA). Analyses included all randomly assigned patients who underwent surgery (Fig 1), an intent-to-treat strategy.

Primary Analyses. We assessed treatment effect by assessing whether the average of individual component treatment effect between groups was zero, adjusted for site (Appendix E2). This strategy avoids the composite being driven by a high-prevalence complication. The strategy also accounted for correlation among individual components of the composite. The trial was not powered to detect differences with respect to any one component of the composite.

Secondary Analyses. Analyses of treatment effect on secondary endpoints are described in Appendix E3.

Results
Patients
From March 2007 to August 2014, 722 patients were randomly allocated to either the 24% or 28% hematocrit trigger. At the second interim analysis (54% of planned enrollment), the trial’s Data and Safety Monitoring Board stopped the study for futility (Fig 2). Five randomized patients were excluded owing to canceled operations, doctor withdrawals before surgery, or protocol violations. Among the remaining 717 patients, 363 were in the 24% hematocrit trigger group and 354 in the 28% trigger group. Six patients withdrew from the study after surgery, but had outcome data recorded and were included for analysis.

Baseline characteristics, clinical factors, and procedures were generally similar between trigger groups (Table 1, Supplemental Table E1).

Primary Endpoints
The primary composite endpoint occurred in 56 patients (16%) in the 24% hematocrit trigger group and 68 patients (19%) in the 28% hematocrit trigger group (Table 2). The estimated average relative effect odds ratio of the 24% versus 28% hematocrit trigger groups was 0.86 (95% confidence interval: 0.29 to 2.54, p = 0.71), which crossed the futility boundary of p = 0.58, suggesting no effect on the composite endpoint (Fig 2). There was no evidence of treatment effect heterogeneity across components of the composite (p = 0.3). There was no statistically significant hematocrit trigger effect at Cleveland Clinic (p = 0.48) or at SAL Hospital (p = 0.68; treatment-by-site interaction p = 0.14), or in any of the sensitivity analyses (Appendix E4).
TREATMENT GROUP AND RBC TRANSFUSION. More patients received transfusion in the 28% trigger group than in the 24% group (75% versus 54%, \(p < 0.0001\); Table 3). That was primarily due to more intraoperative transfusions in the 28% group (59% versus 31%). Median hematocrit at first transfusion was 22% for the 24% trigger group and 24% for the 28% trigger group (Fig 3). In both treatment groups, hematocrit fell to its lowest point during CPB, then rapidly recovered and stabilized after bypass, with the 28% hematocrit trigger group lower on average than the 28% group (Fig 4).

OTHER SECONDARY ENDPOINTS. Hematocrit trigger had no effect on occurrence of prolonged ventilation (more than 24 hours), ICU or hospital lengths of stay, or SF-12 mental or physical component scores between 1 and 3 months (Supplemental Table E2).

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REPORTED FINDINGS
Principal Findings
Randomizing patients to a hematocrit trigger of 24% versus 28% did not affect postoperative morbidity and mortality, lengths of ICU and hospital stay, or quality of life after recovery from surgery. Patients randomly allocated to the 24% trigger group were exposed to higher levels of anemia than the 28% group, but the 28% trigger group was exposed to a greater number of RBC transfusions.

Relationship to Previous Nonrandomized Cohort Studies
Previous cardiac surgery studies report a higher risk of complications for exposure to both lower nadir hematocrit [12] and RBC transfusions [13, 16], with morbidity...
differing by level of exposure [17]. Anemia is undesirable [12, 17–20], as is RBC transfusion [10, 13, 16, 21–25]. Ideally, both exposures should be minimized, but the optimal range of hematocrit values that balances complications of anemia and those of RBC transfusion is unclear, and combined exposure to both is associated with even higher postoperative morbidity [17].

Relationship to Previous Randomized Studies

Hajjar and colleagues [10] randomly assigned patients to liberal (hematocrit trigger 30%) and restrictive (hematocrit trigger 24%) transfusion strategies in the operating room and ICU. As in our trial, the liberal transfusion group received more transfusions than the restrictive treatment group, 78% versus 47%, respectively. Hemoglobin values were slightly higher in the liberal group (10.5 g/dL versus 9.1 g/dL) without a difference in morbidity.

Murphy and colleagues [9] randomly assigned patients exclusively in the postoperative period to a liberal transfusion threshold (hemoglobin trigger 9 g/dL) and a restrictive transfusion threshold (hemoglobin trigger 7.5 g/dL). Transfusion differed between treatment groups: 92% (liberal group) and 53% (restrictive group). Serious morbidity within 3 months and health care costs were similar between groups.

Outcomes of these trials are similar to ours, likely because they were within what Loor and colleagues [20] called the “safety zone” (Supplemental Fig E2), meaning that morbidities from anemia and transfusion were minimized. However, there were some potentially important differences among the three trials. Hajjar and colleagues [10] tracked only transfusion in the operating room and ICU, where most transfusions are given. Murphy and colleagues [9] tracked only ICU and later postoperative transfusions. What differentiates our trial from these is that we transfused according to randomized hematocrit thresholds over the entire continuum of care, from operating room to hospital discharge. These differences in trial design complicate discerning negative results of anemia exposure from those of RBC transfusion. Our prior work found that the lowest hematocrits occurred after initiation of CPB [12], which reflects the intrinsic and predictable acute hemodilution associated with cardiac surgery performed on CPB. That complicates the interpretation of the depth, duration, and safety of this anemia exposure.

Clinical Implications

Reducing the hematocrit trigger to 24% in patients having cardiac surgery did not worsen outcome, but reduced overall RBC use compared with a 28% transfusion trigger. A recent editorial highlighted the complexity underlying recommendations for a uniformly applicable transfusion trigger [1]. Advocates for tolerating lower hematocrit triggers point to reduction in RBC use, whereas others state that additional factors should be considered, such as comorbidity burden, individual organ responses to varying levels of anemia, and acute exposure to hemodilution and blood loss. Paying attention to a study’s lower trigger and the specific population is important, because some investigations advocate higher thresholds in certain populations [26, 27].

Furthermore, there is interplay between lower levels of hematocrit, a patient’s ability to adapt, and a specific organ’s tolerance. Larger percentage reductions in hemoglobin from baseline are associated with worse outcomes

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>HCT Trigger 24% (n = 363)</th>
<th>HCT Trigger 28% (n = 354)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite</td>
<td>59 (16)</td>
<td>68 (19)</td>
</tr>
<tr>
<td>Mortality or multisystem organ failure</td>
<td>3 (0.8)</td>
<td>6 (1.7)</td>
</tr>
<tr>
<td>Neurologic morbidity</td>
<td>1 (0.3)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Pulmonary morbidity</td>
<td>23 (6.3)</td>
<td>19 (5.4)</td>
</tr>
<tr>
<td>Renal morbidity</td>
<td>6 (1.6)</td>
<td>7 (2.0)</td>
</tr>
<tr>
<td>Infectious morbidity</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>36 (10)</td>
<td>50 (14)</td>
</tr>
<tr>
<td>Asystole</td>
<td>2 (0.6)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Gastrointestinal morbidity</td>
<td>5 (1.4)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Reoperative morbidity</td>
<td>9 (2.5)</td>
<td>10 (2.8)</td>
</tr>
<tr>
<td>Vascular morbidity</td>
<td>0 (0)</td>
<td>3 (0.8)</td>
</tr>
</tbody>
</table>

Values are n (%).

HCT = hematocrit.

Table 3. Blood Transfusion and Hematocrit Information

<table>
<thead>
<tr>
<th>Information</th>
<th>No. Pts. a</th>
<th>HCT Trigger 24% (n = 363)</th>
<th>No. Pts. a</th>
<th>HCT Trigger 28% (n = 354)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients receiving transfusion</td>
<td>363</td>
<td>195 (54)</td>
<td>354</td>
<td>265 (75)</td>
</tr>
<tr>
<td>Operating room</td>
<td>360</td>
<td>112 (31)</td>
<td>353</td>
<td>208 (59)</td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>343</td>
<td>105 (31)</td>
<td>336</td>
<td>115 (34)</td>
</tr>
<tr>
<td>Floor</td>
<td>338</td>
<td>41 (12)</td>
<td>318</td>
<td>42 (13)</td>
</tr>
<tr>
<td>HCT when transfusion given</td>
<td>423 b</td>
<td>23 [21, 24]</td>
<td>678 b</td>
<td>25 [23, 26]</td>
</tr>
<tr>
<td>HCT when first transfusion given</td>
<td>203</td>
<td>22 [21, 23]</td>
<td>278</td>
<td>24 [22, 25]</td>
</tr>
</tbody>
</table>

a Patients with data available.  
b More than one transfusion administered to some patients.

Values are n (%) or median [Q1, Q3].

HCT = hematocrit;  No. Pts. = number of patients.
That may relate to an inability to adapt to an acute reduction in hematocrit.

Our trial raises a number of questions related to anemia exposure and RBC transfusion. Could our study results simply reflect equalization of risks of anemia and RBC transfusion (Supplemental Fig E2)? It is recognized that there are lower critical thresholds for hemoglobin values associated with higher morbidity [29] and risks associated with RBC transfusions [13] that describe a U-shaped relationship for the optimal hematocrit “safety zone” where morbidity risk is minimal [20]. The nadir risk describing the boundaries of this zone remain to be established.

Study Limitations

The primary limitation of our trial and others is that low hematocrit and RBC transfusion are inextricably linked except in unusual circumstances. It may be that a higher hematocrit is better if it can be maintained without RBC transfusion. Our trial is silent about whether pharmacologic agents such as preoperative iron supplements or erythropoietin, or operative interventions such as hemocentration or cell salvage, would provide different results. Furthermore, the ability to extrapolate findings from other settings is problematic: chronic anemia in medical patients may be different from that in the perioperative setting, in which patients are exposed to an acute reduction of hematocrit in addition to other negative exposures, such as extensive incisions, CPB, hypothermia, and blood loss.

The two thresholds chosen for this trial—hematocrit trigger of 24% versus 28%—represented the area of surgeon equipoise at the two participating institutions. These do not represent extremes of clinical practice, and thus limited our ability to resolve differences in endpoint outcomes.

During the trial, a concerted effort was made to decrease morbidity and mortality after cardiac surgery. As a result, we observed a 19% occurrence of these events, far lower than the 35% historical prevalence on which we based sample size for the trial. Therefore,
empirical power was only 59% for the overall analysis for the planned relative risk of 0.75 (Appendix E1). This reduction in adverse events across time should not have affected one trigger group versus the other because of block randomization.

The trial was not powered for any individual complications of surgery, which would have required a sample size far greater than in the present trial. That led to the use of a composite primary endpoint. However, unlike the typical composite endpoint that can be dominated by the most frequently occurring event, we used novel statistical methods that eliminated the problem and also accounted for correlation among composite components (see Appendix E2).

The two institutions represent practices in two different countries, and different patient characteristics necessitating analyses of interactions and sensitivity analyses. Each institution was separately randomized to prevent unintentional institutional imbalances between study arms.

Finally, the Consolidated Standards of Reporting Trials flow diagram (Fig 1) reflects the challenges of conducting a trial of transfusion triggers. Nearly 60% of patients screened for the trial were not randomized because they were not expected to receive transfusions; others were not randomized because of off-pump surgery. These same challenges have been encountered in transfusion trigger trials both outside [30] and within cardiac surgery settings [10, 31].

Conclusion

Patients assigned to a transfusion hematocrit trigger of 24% had more anemia, whereas patients allocated to a 28% trigger required more transfusion. Both exposures are potentially harmful, and we cannot distinguish their independent effects. Nonetheless, postoperative complications and lengths of stay were similar in the two groups, suggesting balanced risk. We therefore advocate the lower transfusion threshold, because it supports blood conservation efforts without increasing adverse events.

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References


