Intraoperative Anemia and Single Red Blood Cell Transfusion During Cardiac Surgery: An Assessment of Postoperative Outcome Including Patients Refusing Blood Transfusion

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Objectives: **Increasing evidence suggests benefits from restrictive red blood cell transfusion (RBC) thresholds in major surgery and critically ill patients. However, these benefits are not obvious in cardiac surgery patients with intraoperative anemia. The authors examined the association between uncorrected hemoglobin (Hb) levels and selected postoperative outcomes as well as the effects of RBCs.**

Design: **Cohort study with prospectively collected data from a cardiac surgery registry.**

Setting: **A major cardiac surgical hospital within the Netherlands, which is also a referral center for Jehovah's Witnesses.**

Participants: **Patients (23,860) undergoing cardiac surgery between 1997 and 2013.**

Interventions: **Comparisons were done in patients with intraoperative nadir Hb <8 g/dL and/or an Hb decrease $\geq 50\%$. Comparison (A) between Jehovah's Witnesses (Witnesses) and matched non-Jehovah's Witnesses (non-Witnesses) transfused with 1 unit of RBC, and comparison (B) between patients given 1 unit of RBC intraoperatively versus matched non-transfused patients.**

Measurements and Main Results: **Postoperative outcomes were myocardial infarction, renal replacement therapy, stroke, and death. With propensity matching, the authors optimized exchangeability of the compared groups. Adverse outcomes increased with a decreasing Hb both among Witnesses and among non-Witnesses. The incidence of postoperative complications did not differ between Witnesses and matched non-Witnesses who received RBC (adjusted odds ratio 1.44, 95% confidence interval 0.63-3.29). Similarly, postoperative complications did not differ between patients who received a red cell transfusion and matched patients who did not (adjusted odds ratio 0.94, confidence interval 0.72-1.23).**

Conclusion: **Intraoperative anemia is associated with adverse outcomes after cardiac surgery, and a single RBC transfusion does not seem to influence these outcomes.**

KEY WORDS: anemia, Jehovah's Witnesses, cardiac surgery, red blood cell transfusion, postoperative outcomes

BOTH LOW intraoperative hemoglobin (Hb) concentration and red blood cell (RBC) transfusions have been associated with adverse outcomes after cardiac surgery.[1–4] Results from randomized controlled trials performed in patients with various medical conditions, usually using 7.0 or 8.0 g/dL as a restrictive transfusion threshold, suggested no beneficial effects of a more liberal transfusion strategy.[5–7] Clinical guidelines increasingly promote lower transfusion triggers despite insufficient evidence in cardiac surgery regarding the intraoperative Hb level at which the beneficial effects of RBC transfusions outweigh the risks.[8–13]

The interpretation of the association between Hb concentrations and clinical outcomes is hampered by the effect of RBC transfusions, since with decreasing Hb concentrations more patients will be treated with transfusions. RCTs cannot investigate this topic in severely anemic patients as withholding transfusion in these patients is widely considered unethical. Patients who decline transfusion for whatever reason (for example Jehovah's Witnesses, further abbreviated as Witnesses) enable clinicians to study the association between Hb decrease and relevant postoperative outcomes in the absence of RBC transfusions. Comparing anemic Witnesses with transfused anemic non-Jehovah's Witnesses (non-Witnesses) undergoing cardiac surgery can provide valuable information about the consequences of uncorrected anemia or the benefits of transfusion.

Previous studies with Witnesses showed an increase in morbidity when the Hb level decreased below 8 g/dL, and an increased mortality when the Hb level decreased below 7 g/dL.[4,14] However, cardiac surgery was not specially addressed in these studies. Cardiac surgery studies including Witnesses underscored the good outcome and similar mortality and morbidity rates as in non-Witnesses, provided Hb levels were optimized.[15–17] However, the postoperative outcomes of Witnesses undergoing cardiac surgery and suffering from an intraoperative Hb decrease below 8g/dL (and thus reaching a possible harmful Hb level) have not been reported.

The authors hypothesized that uncorrected anemia would lead to more postoperative complications and that RBC transfusions would help decrease these complications. The authors' objectives were to describe the association between intraoperative Hb and postoperative adverse events among patients who received no RBC transfusions during cardiac surgery in both Witnesses and non-Witnesses. Furthermore, Witnesses who, based on intraoperative anemia (intraoperative nadir Hb <8 g/dL and/or Hb decrease $\geq 50\%$), would be eligible for RBC transfusion were compared to similar anemic non-Witnesses who received a single RBC transfusion. Because unidentified differences in preoperative selection and intraoperative treatment between Witnesses and non-Witnesses may have occurred, the authors composed an additional (non-Witness only) study cohort of anemic patients in which they

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compared non-transfused patients with patients who received 1 unit of RBC.

METHODS OF STUDY AND DESIGN

This study complied with the Declaration of Helsinki (10th version, 2012-2013). The local research ethics committee approved this study, and the need for informed consent was waived.

Study Setting

The analyses were performed with data of a single-center cardiac surgery registry. Details of this registry have been described earlier.[13] In this registry, perioperative data, including morbidity and process as well as outcome indicators, from all consecutive patients who undergo cardiac surgery in the Amphia Hospital, Breda, the Netherlands are collected. Data collection for the present analysis took place between January 1, 1997 and January 1, 2013 and was compliant with the Dutch National Cardiac Surgery Registry (BHN) and the Dutch National Intensive Care Registry (NICE, instituted since 1996).[18] All data were acquired from preoperative, intraoperative, and postoperative routine blood collections and medical files. Data regarding blood transfusion were obtained from the hospital laboratory information system.

Since 2006, a Patient Blood Management Program (PBMP) is in place covering the complete perioperative period (including ICU and ward). This PBMP is compliant with the transfusion guidelines of the American Society of Anesthesiologists, the Dutch transfusion guidelines and, more specifically, the guidelines from the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists (STS and SCA guidelines published in 2006 and updated in 2011).[19–21] Intraoperatively, an Hb trigger of 8.0 g/dL is used. During cardiopulmonary bypass, Hb above 7.0 g/L is maintained either by transfusion or hemoconcentration, whatever is most appropriate according to the attending anesthesiologist.

Since 2009, this PBMP was further expanded with more elaborated coagulation monitoring and component therapy (Point-of-Care Coagulation, Rotem ®, TEM, Inc.). Within the Netherlands, the Amphia Hospital is a major referral center for Witnesses undergoing cardiac surgery. Witnesses are operated according to a local protocol prohibiting any transfusion of blood products. The differences between PBMP in Witnesses and non-Witnesses are presented schematically in the Appendix.

Study Population

To study the association between intraoperative Hb and adverse postoperative outcomes, all patients who underwent cardiac surgery between 1997 and 2013 (Witnesses and non-Witnesses) were included.

To assess the possible effect of RBC transfusion on postoperative outcome, the authors performed 2 separate analyses. First, they compared Witnesses with transfused non-Witnesses (Comparison A); second, they compared transfused with non-transfused non-Witnesses in a different study cohort (Comparison B).

Comparison A

All anemic Witnesses who, according to current guidelines, could have benefitted from intraoperative RBC transfusion were identified. For that purpose the authors defined anemia as an intraoperative Hb <8 g/dL and/or an Hb decrease $\geq 50\%$. The authors chose this double threshold based on current literature and because a previous study of their research group showed that patients who had an Hb decrease of 50% or more had a significantly higher chance of adverse outcome. The authors assumed that patients with an intraoperative Hb decrease of $>50\%$ would equally benefit from an RBC transfusion as patients with an Hb level below 8 g/dL.[13] Witnesses were matched to non-Witnesses who received 1 RBC unit intraoperatively. The authors selected patients who received 1 RBC unit because comparability between patients who receive none and patients who receive multiple RBC is poor. To prevent selection bias, all non-Witnesses receiving a single RBC were considered possible matches regardless of whether they had received platelet/FFP transfusion or not. If the authors only included non-Witnesses who had received one RBC and no other blood products, they would have ignored the fact that Witnesses also could have been in need of a transfusion with additional blood products.

Since the introduction of the PBMP in 2006, basic intraoperative blood-sparing measures in non-Witnesses have become similar to those in Witnesses. However, the authors acknowledge that Witnesses may undergo a more careful preoperative selection and preparation while, intraoperatively and postoperatively, the cardiac surgical team may work more cautiously to limit blood loss. This may introduce bias or other unidentified benefits that compromises the comparability of Witnesses and non-Witnesses.[15–17,22–24]

Comparison B

In order to cope with these identified and unidentified biases when comparing Witnesses, the authors designed an additional comparison of non-Witnesses. Here, the authors compared non-transfused patients with propensity-matched patients who received a single intraoperative RBC transfusion in the absence of any additional blood products (because in this cohort this would not introduce a selection bias). Data were available on whether the RBC transfusions had been administered during surgery, in the ICU, or on the surgical ward. This information, however, did not allow a distinction between intraoperative RBC transfusion during the primary cardiac operation and a possible subsequent re-sternotomy. The authors, therefore, excluded patients who had undergone a re-sternotomy.

Exposure and Outcome Definitions

The lowest intraoperative Hb was taken as the nadir Hb. The Hb decrease in percent was calculated as follows:

$$[(\text{preoperative Hb} - \text{nadir Hb})/\text{preoperative Hb}] \times 100.$$

Intraoperative Hb was measured routinely according to institution protocol after induction of anesthesia, 30 minutes after the start of cardiopulmonary bypass (CPB) (after cardioplegia) and after heparin reversal before chest closure.