Author’s response to reviews

Title: Intra-operative red blood cell transfusion and mortality after cardiac surgery

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Author’s response to reviews:

Dear dr. Scarlatescu,

We thank the reviewers Patrick Meybohm and Mohammad Reza Rasouli for the time to review our manuscript entitled “Intra-operative red blood cell transfusion and mortality after cardiac surgery”.

In this paper, we report on the investigation of the association between intraoperative red blood cell (RBC) transfusion and mortality in patients undergoing coronary surgery. Propensity score (PS) analysis was used and represented the likelihood of receiving RBC transfusion based on pre- and intraoperative characteristics. To define risk subgroups, patients were stratified into four groups of equal size based on the sample distribution of the PS. A subgroup analysis was performed in the group of patients at highest risk of RBC transfusion.

During answering the questions of the reviewers there appears to be a type of error in the results, page 7, row 162. The correct result is that in patients with the highest probability of transfusion intraoperative RBC transfusion was associated with a 4.1-fold risk of mortality (PS adjusted OR 4.1 and 95% CI 1.3-12.6, P=0.016)

We believe that this manuscript is appropriate for publication by BMC because red cell transfusion is essential for successful cardiac surgery. This study demonstrates that patient subgroups may benefit from a restrictive transfusion practice. Further insight in the risk of intra-operative RBC transfusion to treat anaemia may aid cardiac anesthetists to further improve perioperative patient blood management.
Our point-by-point response to the comments from the reviewers is added as attachment to this letter. All changes are marked in the revised documents.

We have no conflicts of interest to disclose.
Please address all correspondence concerning this manuscript to me at e.vlot@antoniusziekenhuis.nl. Thank you for your consideration of this manuscript.

Sincerely, on behalf of all the authors,

Eline Vlot

Answers to the reviewers;

We thank Patrick Meybohm and Mohammad Reza Rasouli for their time to review our manuscript. All changes are marked in the revised documents.

Patrick Meybohm (Reviewer 1)

I really much appreciate to review this fascinating manuscript. The topic is very important, study design and analyses are adequate, the presentation of study results and discussion are impressive.
I recommend to accept this paper with the following minor modification:
Please add the data for allogeneic transfusions of plasma, platelets, coagulation factors, and number/rate of patients with massive bleeding/massive transfusion.

The following changes have been made in the manuscript;
In results, page 6, row 130; the heading is changed in; "Intraoperative transfusions"
In results, page 6, row 127 the following massive bleeding data have been added; " In 3% of patients drain production exceeded 2000ml/12 h."
In results, page 6, row 131, the following transfusion data have been added to the results; " A total of 647 (22%) patients received a median of 3 [2-4] units of any intraoperative allogeneic transfusion. Plasma transfusion occurred in 210 patients (7%) with a median of 2 [2-2] units and platelet transfusion was performed in 567 patients (19%) with a median of 1 [1-2] units."

Mohammad Reza Rasouli, MD (Reviewer 2)

Association with intraoperative RBC transfusion and postoperative adverse outcomes including mortality has been shown in various types of surgeries including cardiac surgery and study findings are not novel. However, this study can be considered as an additional piece of data.

We agree with doctor Rasouli that the reported association between RBC transfusion and mortality is not new. However, in our opinion the paradox that both anemia and transfusion are associated with adverse outcome in cardiac surgery patients cannot be emphasized enough.
Despite progress made in defining the optimal transfusion practice, the optimal transfusion trigger in cardiac surgery patients is fairly unknown. Our paper provides further insight in the risk of intraoperative RBC transfusion to treat anaemia and may aid cardiac anesthetists to further improve perioperative patient blood management.

I was wondering why the authors included patients who had AVR in the study. As the authors know, valve replacement is an entirely different procedure from CABG and including AVR in the cohort makes the cohort heterogenous. The other question is that why authors included CABG+AVRs and did not include patients who needed CABG and MVR? Also there were some patients who had previous cardiac surgery and they were included too. Resternotomy is associate with a high risk of bleeding and including these patients in the cohort does not sound appropriate. In other word, the study cohort is heterogenous.

We agree that there is a difference in associated risk for RBC transfusion between CABG and CABG + AVR surgery. Although adding AVR (and previous cardiac surgery and resternotomy) patients to our cohort makes it heterogeneous, we believe it is important to present data that represent real world practice to estimate the effects of treatment on outcome. We used PS analysis to account for systematic differences in baseline characteristics and show that CABG + AVR surgery increased risk for RBC transfusion associated mortality. In our data, after stratification into quartiles according to PS, mortality and transfusion were highest in Q4. After adjustment for differences in age, EuroSCORE, preoperative Hb, type and duration of surgery, resternotomy was not significantly associated with mortality (OR 2.0, 95% CI 0.87-4.72, P=0.10)

*This study covers more than 3 years. I was wondering if there was any significant changes in mortality or transfusion rate during the study period.

Change-point analysis on postoperative mortality during the study period revealed no change-point detected for postoperative mortality. For RBC transfusion a change-point was detected at Q1 2015 with >98% confidence showing a decrease in RBC transfusion rate since TEG was implemented as part of our intraoperative patient blood management.

*Regardless of Hct level, hemodynamic instability is another indication for intraoperative RBC transfusion. I was wondering if intraoperative TEE and/or PA catheter was used for hemodynamic monitoring in the study patients.

No PA catheter is used for hemodynamic monitoring during surgery in our hospital.

Intraoperative TEE is routine procedure during valve surgery. In isolated CABG, use of TEE monitoring was left to the discretion of the attending anesthetist during study period. Nowadays TEE is routine procedure in all cardiac surgery patients.

*It seems that intraoperative FFP transfusion was performed subjectively based on amount of blood loss or signs of coagulopathy rather than using lab data (fibrinogen, coags or TEG). That should be mentioned as a study limitation.

Since Q2 2015 TEG was part of our local transfusion protocol.

In Methods, blood transfusion management, page 4, row 88, we mention that "point-of-care hemostatic monitoring was implemented in Q2 of 2015 as a part of routine blood management."
* It is recommended to adjust study findings for other blood products (FFP, cryo or platelet) that administered intraoperatively.

The plasma and platelet transfusion data have been added to the document:

In results, page 6, row 131 we added; ‘’A total of 647 (22%) patients received a median of 3 [2-4] units of any intraoperative allogeneic transfusion. Plasma transfusion occurred in 210 patients (7%) with a median of 2 [2-2] units and platelet transfusion was performed in 567 patients (19%) with a median of 1 [1-2] units.”

Cryoprecipitates are not used in our hospital. Multicollinearity exists between transfusion products. Based on clinical judgement RBC transfusion is representative for transfusion. With the retrospective analysis of our data we would like to focus on the risk of intra-operative RBC transfusion because intraoperative RBC transfusion is often part of anaemia treatment while plasma and platelets are used to correct coagulopathy.

In the whole study cohort OR for RBC associated mortality changes with 6% after adding plasma transfusion to the PS adjusted mortality (OR 3.1, p 0.003 >> OR 2.9, p0.005). In Q4, OR for RBC associated mortality changes with 7% after adding plasma transfusion to the PS adjusted mortality (OR 4.1, p0.016 >> OR 3.8, p0.021). Platelet transfusion is excluded because this is not significantly associated with mortality in both regression analyses.

*It would be useful if authors could report etiology of death in their cohort.

We agree with dr. Rasouli that it would be of great interest to analyze the etiology of death.

However, if postoperative patients are meeting discharge criteria they are transferred to their referring hospital within a few days after surgery.

Unfortunately data about etiology of death were not registered in the national registry of cardiac interventions.