Author's response to reviews

Title: Should we restrict erythrocyte transfusion in early goal directed protocols?

Authors:
Patrick Meybohm Prof. Dr. (patrick.meybohm@kgu.de)
Aryeh Shander Prof. Dr. (Aryeh.Shander@ehmc.com)
Kai Zacharowski Prof. Dr. Dr. (kai.zacharowski@kgu.de)

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Author's response to reviews: see over
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Dear Prof. Kienbaum,

Thank you very much for the transmission of the reviewers’ comments on our paper “Should we restrict erythrocyte transfusion in early goal directed protocols?” and for giving us the opportunity to revise the manuscript.

Below, we provide a detailed point-by-point response to the editors’ and reviewers’ comments.

We very much look forward for your response,
Respectfully

Patrick Meybohm
Point-by-point answer

Editor

In face of the most recent work by Murphy (NEJM 2015; 372: 997-1008) I also recommend discussing acceptable hemoglobin concentrations in specific patient groups in greater detail.

We are appreciating this important comment and added to the revised manuscript: “In high-risk cardiac surgical patients, Murphy et al. [7] recently randomly assigned 2,007 patients post cardiac surgery (they were either revascularized or replaced defective valves) to a restrictive transfusion threshold (hemoglobin level <7.5 g/dl) or a liberal transfusion threshold (hemoglobin level <9 g/dl) group. The primary outcome was a serious infection (sepsis or wound infection) or an ischemic event (permanent stroke, myocardial infarction, infarction of the gut, or acute kidney injury) within 3 months after surgery. Transfusion rates were 53.4% (higher than many liberal transfusion hospitals) and 92.2% in the two groups, respectively. The restrictive transfusion threshold was not inferior to the liberal threshold with respect to morbidity or 30 day mortality. Mortality at 90 days was statistically higher in the restrictive group with 16 more deaths than in the liberal-threshold group. These finding are perplexing since the causes of death were not related to anemia and no plausible mechanism was offered by the authors. In this respect, this study provides non-inferiority data on restrictive transfusion and should not result in change of practice until these findings are either corroborated or refuted. It is also unclear whether the liberal transfused group were benefiting from the ‘volume therapy’ which the restrictive group has not received.”

Reviewer 1

The conclusion statement requires some revisions. It is true that the role of RBC transfusion to maintain hematocrit ~30% in EGDT has not been extensively evaluated, but this does not lead to a conclusion that a PBM needs to be in place. There needs to be more evidence to support the use of PBM in critically ill patients. The authors can suggest that a PBM could be adopted in EGDT, but the threshold may need to be more individualized.

According to these comments, we have re-phrased the Conclusion section – “a PBM program employing multiple strategies to minimize unnecessary exposure to blood products could be adopted within EGDT protocols. Additionally, transfusion thresholds for RBC transfusion need to be more individualized.”

Were all references in Table 1 included in the reference list?

We have changed the reference list.

The title may be changed to something like "Should we restrict erythrocyte transfusion in early goal directed protocols?"

We have changed the title based on this reviewer’s suggestion.

Reviewer 2

No comments. Well written comment.

Nice.

Reviewer 3

The authors address an important problem of interest, namely the integration of Patient Blood Management (PBM) into the early goal directed therapy (EGDT). To focus on PBM within EGDT is a good thing and using restrictive triggers are usually a good first step to implement PBM. However, I have some major concerns:

1. The title refers to the use of transfusion triggers within EGDT protocols. In the abstract (p2), the study question is stated as: “could EGDT bundles have better outcome if a restrictive transfusion practice is adopted?” Then the authors discuss this issue and refer to published studies regarding triggers. However, in the conclusion the authors add a remark on a PBM program employing multiple strategies”. The latter is only scarcely discussed in the text and not supported by studies. The only conclusion that can be made is that a restrictive transfusion trigger may be appropriate in this context.
We apologize if the abstract, main text and conclusion have not fully been conclusively. Therefore, we have deleted “multiple strategies” and re-phrased the Conclusion section: “...a PBM program to minimize unnecessary exposure to blood products could be adopted within EGDT protocols. Additionally, transfusion thresholds for RBC transfusion need to be more individualized.”

Another thing that was not clear to me was that “autologous blood transfusion” was stated as one of the key words. Together with the remark in the conclusion that a PBM program employing multiple strategies to minimize exposure to blood products should be the new standard of care” (p4), I believe the authors would like to go a step further with the use of autologous blood as blood saving alternative, however, this is not discussed further in the paper at all. Could the authors be more specific on this issue what they mean by this PBM program?

We apologize, as abstract, main text and conclusion were not fully conclusively. Key words were changed to “allogeneic blood transfusion”. In this commentary paper we’d like to focus discussion on transfusion triggers within early goal directed therapy protocols, rather than on alternative strategies, e.g. autologous blood transfusion.

2. The authors should also discuss the published evidence for autologous transfusions in the text if they include these as a strategy in their PBM program, including its cost-effectivity.

Key words have been changed to “allogeneic blood transfusion”.

3. The authors mention the group of high-risk surgical patients to which the EGDT has expanded on p. 2. It is not clear to me if the authors intended to have a specific group in mind for which the PBM program is most suitable for. I expect this may be the elective high risk surgery patients, since the concept of PBM programs originates from elective surgery. Please elucidate.

We have re-phrased the Introduction section as follow: “…EGDT was adopted for high-risk surgical patients, e.g. cardiac surgery patients [Aya HD, Cecconi M, Hamilton M, Rhodes A. Goal-directed therapy in cardiac surgery: a systematic review and meta-analysis. Br J Anaesth. 2013; 110:510-7]. In this respect, EGDT plays an important role in both critical care patients and in surgical patients, at least in the higher-risk population. Regarding the role of PBM within EGDT protocols, we think that PBM might be a key element to minimize unnecessary exposure to blood products, irrespective of elective or unplanned surgery.

4. A Hb level of 8 g/dL and a Ht of 30% are not the same. What trigger do the authors find appropriate to use in their PBM program?

In this paper, we would like to caution the reader that most of the published EGDT protocols recommend “transfusion of RBC targeting hemoglobin >8g/dL or hematocrit level > 30% as a key element to increase central venous oxygen saturation.”

But importantly, “thresholds for RBC transfusion need to be more individualized”. Therefore, we cannot give final recommendations for appropriate triggers within PBM programs.