Author's response to reviews

Title: Red blood cell transfusion in patients with traumatic brain injury: a systematic review protocol

Authors:

Amélie Boutin (amelie.boutin.2@ulaval.ca)
Michael Chassé (michael.chasse@gmail.com)
Michèle Shemilt (michele.shemilt.1@ulaval.ca)
François Lauzier (francois.lauzier@med.ulaval.ca)
Lynne Moore (lynn.moore@fmed.ulaval.ca)
Ryan Zarychanski (Ryan.Zarychanski@cancercare.mb.ca)
Jacques Lacroix (j_lacroix@videotron.ca)
Dean A Fergusson (dafergusson@ohri.ca)
Philippe Desjardins (philippe.desjardins.1@ulaval.ca)
Alexis F Turgeon (Alexis.Turgeon@fmed.ulaval.ca)

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Author's response to reviews: see over
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David Moher, Paul G Shekelle, Lesley A Stewart
Editors-in-chief

Systematic Reviews
c/o BioMed Central
236 Gray's Inn Road
London WC1X 8HB
United Kingdom

Re: Red blood cell transfusion in patients with traumatic brain injury: a systematic review protocol

Dear Drs Moher, Shekelle and Stewart,

On behalf of my co-authors, I am submitting a revised version of the manuscript of our protocol to the Systematic Reviews. We made some corrections according to the reviewer’s comments and editor suggestions. I attest to the fact that all co-authors agreed to the submission of the reviewed manuscript to the Systematic Reviews.

Sincerely,

Amélie Boutin MSc,
PhD candidate in Epidemiology
Department of Social and Preventive Medicine, Université Laval

Population Health and Optimal Health Practices Research Unit
Trauma - Emergency - Critical Care Medicine
CHU de Québec Research Center (Hôpital de l'Enfant-Jésus)
1401, 18e rue, local H-040, Québec (Québec), G1J 1Z4
Phone: (418) 649-0252 #4056
Fax: (418) 649-5733
Email: amelie.boutin.2@ulaval.ca
Response to Reviewers

First, we want to thank the reviewer for his valuable comments. We addressed the reviewers’ comments point-by-point and described the changes made in the above section. All changes to the manuscript are highlighted.

1. the project is interesting, but this is only the methodology - where are the results?
   This is the protocol of a systematic review. Therefore, no results are reported.

2. the amount of RBC transfused should be normalized to the number of days spent in the ICU;
   Unfortunately, as we work with published data (usually aggregated), we cannot take into account the exact number of days for each patient, and thus preventing normalization to the number of days spent in the ICU or the use of rates (number of events / time spent in the study population). We have planned to conduct analysis by subgroup of studies reporting RBC transfusion over comparable period of time (e.g., emergency department stay, ICU stay, hospital stay). We are aware that it represents an approximate timing and that there is a possible survival bias when looking at the association between transfusion and outcomes that is difficult to control for. Considering your comment, we added a subgroup analysis according to the mean or median number of days considered, when available.

3. it would be nice to examine subgroups according to comorbidities +/- a) heart disease (CAD); b) chronic renal failure; c) cancer
   Since we conduct a systematic review using aggregated data, we do not expect to obtain the required data to take into account the impact of comorbidities in our analyses. However, we added a subgroup analysis according to comorbidities. This will be feasible if results of included studies are reported according to comorbidity subgroups or if individual patient data are available.

4. it would be nice to better specify which complications will be looked for and how they will be reported (as groups; one by one etc.)
   We added a list of variables in appendix 2. We will collect data on any complication reported in the included study (published data). We will analyse complications as a dichotomous variable (presence or absence of any complications), and individually (presence or absence of specific complications) or according to complication categories (as per previous work from our team: Ann Surg 2014;259(2):374-80). We specified this information in the ‘Summary measures’ section.

5. classification of "severe" TBI could be improved (we assume it will be on GCS - any data on Marshall score on CT-scan ?)
Severity for subgroup analysis will be based on reported GCS. Having conducted multiple systematic reviews on traumatic brain injuries, we expect the severity to be reported mainly with GCS, with very few studies using other scales such as head AIS. Using aggregated data, we will consider the minimal level of severity used for inclusion to categorize the TBI severity. We could also use the mean or median GCS, but considering the expected variability of the range, we chose to evaluate the impact of severity using the minimal severity for inclusion only. It will allow understanding how limiting inclusion to severe TBI only, for example, can impact on the frequency of RBC transfusion and the effect size of the association between transfusion and outcomes.

6. better define "unfavorable neurological outcome" - on GOS? mRamkin?
We will collect data on any scale used to evaluate neurological outcome.

7. correct for bleeding
We probably won’t be able to correct for bleeding due to the type of data reported in published studies. However, we added secondary analyses taking into account if bleeding was reported and analysing the impact of bleeding by subgroups analyses.

8. is it possible to retrieve for some studies the IMPACT score (which predicts mortality at 6-months), the authors could then compare the predicted with the observed mortality in the sub-groups of patients according to the total number of RBC received or to their RBC/ICU days ratio.
We do not expect to be able to conduct such accurate analysis, as we will have to work with published aggregated data. However, we added the CRASH and IMPACT scores to our extraction form and subgroups analysis according to IMPACT and the CRASH scores, if possible to be performed.