Dear Dr. Whitlock

Manuscript ID BMJ.2015.024783 entitled "Harms associated with single-unit perioperative transfusion: a retrospective cohort study"

Thank you for sending us this paper, which we were pleased to have the chance to consider, and enjoyed reading. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it. This is because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. Looking forward to hearing from you again and, we hope, to reaching a decision.

Deadline: Your revised manuscript should be submitted within 6 to 8 weeks

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You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer.

Once the revised manuscript is prepared, you can upload it and submit it through your Author Center. When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) and Committee in the space provided. You can use this space to document any changes you make to the original manuscript and to explain your responses. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Many thanks again. We look forward to seeing your revised article within 6 to 8 weeks.

Yours sincerely

Georg Roeggla

groggla@bmj.com
**Report from the BMJ’s manuscript committee meeting**

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Manuscript meeting 26.03.2015

Elizabeth Loder (chair), Julie Morris (stats), Kristina Fister, Georg Roggla, Alison Tonks, Wim Weber, Tiago Villanueva, Rebecca Burch, Rubin Minhas, 2 guests

Decision: Ask for revision

The committee was interested in the topic of your research. The following concerns were mentioned:

- The committee shared the reviewers concerns.
- The major issue as with all database studies is the inability to determine causality.
- What does your paper add to previous publications on this topic?
- Please provide a clear and robust message for general readers.
- Isn’t it just as possible that the need for more units of pRBCs is a marker for underlying surgical or medical complexity and it’s that factor increases the risk of these outcomes?
- Please be specific about the types of stroke.

First and foremost, please revise your paper to respond to all of the comments by the reviewers. Their reports are available below. Please also respond to the additional comments by the committee.

**IMPORTANT**

When you revise and return your manuscript, please take note of all the following points. Even if an item, such as a competing interests statement, was present and correct in the original draft of your paper, please check that it has not slipped out during revision.

a. In your response to the reviewers and committee please provide, point by point, your replies to the comments made by the reviewers and the editors, and please explain how you have dealt with them in the paper. It may not be possible to respond in detail to all these points in the paper itself, so please do so in the box provided

b. If your article is accepted it will then be edited, proofed, and after your approval published on bmj.com with open access. This open access Online First article will not be a pre-print. It will represent the full, citable, publication of that article. The citation will be year, volume, elocator (a unique identifier for that article): eg BMJ 2008;337:a145 — and this is what will appear immediately in Medline, PubMed, and other bibliographical indexes. We will give this citation in print and online, and you will need to use it when you cite your article.

c. Please write an abridged version of the article for the print and iPad BMJ using the appropriate BMJ pico template for your study’s design. Please be reassured that it doesn’t take long to complete this. When your BMJ pico is ready please email it to papersadmin@bmjgroup.com. The templates for you to download are at http://resources.bmj.com/bmj/authors/bmj-pico

Please include the items below in the revised manuscript to comply with BMJ style:

* the title of the article should include the study design eg "a retrospective analysis of hospital episode statistics"

* ID of ethics committee approval and name of the ethics committee/IRB; or a statement that approval was not required (see http://resources.bmj.com/bmj/authors/editorial-policies/guidelines)

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further data available, please use this wording: "Data sharing: no additional data available"

* please write the discussion section of your paper in a structured way, to minimise the risk of careful
explanation giving way to polemic. Please follow this structure:
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- strengths and weaknesses in relation to other studies, discussing important differences in results and
what your study adds. Whenever possible please discuss your study in the light of relevant systematic
reviews and meta-analyses (eg Cochrane reviews)
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* summary statistics to clarify your message

We do want your piece to be easy to read, but also want it to be as scientifically accurate as possible. Please include in the results section of your structured abstract (and, of course, in the article’s results section) the following terms, as appropriate:

For a clinical trial:
• Absolute event rates among experimental and control groups
• RRR (relative risk reduction)
• NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000)

For a cohort study:
• Absolute event rates over time (eg 10 years) among exposed and non-exposed groups
• RRR (relative risk reduction)

For a case control study:
• OR (odds ratio) for strength of association between exposure and outcome

For a study of a diagnostic test:
• Sensitivity and specificity
• PPV and NPV (positive and negative predictive values)

For research articles

As well as submitting your revised manuscript, we also require a copy of the manuscript with changes highlighted. Please upload this file with file designation 'Revised Manuscript Marked copy'.

REFEREES COMMENTS

Reviewer: 1

Recommendation:

Comments:

The authors of this study performed a retrospective analysis of administrative data collected by Premier Inc. with the goal to determine if the perioperative transfusion of blood was associated with adverse outcome, specifically MI/stroke. They hypothesized that “transfusion of as little as 1 unit of pRBCs in the operating room or the day following would be associated with measurably increased odds for perioperative stroke and myocardial infarction (MI).” They concluded that indeed the transfusion of blood in the perioeprative period was associated with increased odds for stroke and/or MI.

The topic is interesting and clinically relevant. The manuscript is well written and the methods are well described. The abstract conveys the main message.

However, there are a number of issues that I would like to see addressed by the authors:

The major issue, as with all database studies is the inability to determine causality. The authors rightfully speak of associations (and not causality), but nevertheless in the case of blood transfusions the question has to remain if the transfusion of blood is just a surrogate marker for other variables determining adverse outcome. In this context administrative databases such as Premier lack crucial clinical detail such as the amount of blood loss, hematocrits, transfusion triggers used, invasiveness of the procedure, the occurrence of interoperative surgical complications, length of operation times, hemodynamic details and level of patient comorbidity burden. Even if some information is available, it is often presented in binary form (i.e. present or not via the ICD9 coding system), thus not allowing for determination of the severity of the condition. This is not to say that because of this, all studies utilizing databases are "not useful". Quite the opposite is the case, especially when crucial observations have not yet been reported in the literature and/or cannot be obtained from clinical trials, databases can present a first look into a subject matter that can then lead to the formation of further hypotheses. In the case of blood transfusions, however, much evidence has been published on the ill-effects of liberal transfusion practices (although as the authors suggest data specifically for MI and stroke outcomes may be less common). Thus, the ability of the results from this study to add significant knowledge is limited. For example, without knowing which of these transfusions could be considered appropriate and which not (which is impossible without knowing any laboratory values, hemodynamic parameters and other clinical detail) conclusion that can be drawn are limited. The issue of using databases such as Premier for the topic of perioperative blood transfusions is particularly challenging (see Blood transfusions in total hip
and knee arthroplasty: an analysis of outcomes. Danninger T, Rasul R, Poeran J, Stundner O, Mazumdar M, Fleischut PM, Poultsides L, Memtsoudis SG ScientificWorldJournal. 2014 Jan 21;2014:623460. In this publication, the same database was used to look into the particular problem of perioperative transfusions and various outcomes, and encountered multiple problems/limitations. While insights were gained into practice patterns, the inability to address the issue of cofounding had to be acknowledged and limited interpretations. Thus the authors should present a very convincing and strong argument regarding the novelty and additional importance of their study to the field.

Other comments:

1) Having mentioned the issue regarding the lack of the ability to establish causal relationships, did the authors consider that actual effect in their model would be the surgical intervention, stroke/MI the outcome and that the transfusion would function as a moderator? Would it be feasible to employ methodological methods to take this relationship into account?

2) The authors present a possible pathophysiologic process by which transfusions may lead to adverse outcomes. This should be lauded and is important. In the case of MI/stroke and other cardiovascular problems however, other mechanisms are equally plausible. Anemia and resulting hypotension may be additional factors, which in this case may be the trigger for blood transfusions. This should be more thoroughly discussed.

3) Did the authors consider evaluating the use of blood conservation methods, like cell saver, the use of colloids, use of anticoagulants/platelet agents and the utilization of resources such as ICUs? All these factors may affect the outcome or choice to transfuse PRBCs and are available in Premier.

4) The authors present in their methodology an attempt to control for hospital level variables, but it remains unclear if they just include hospital type information or actually performed a multilevel analysis accounting for each individual hospital, which may take into account differences in local practice patterns.

5) While the attempt to control for present on admission comorbidities is laudable, from my experience this variable has a high missingness in Premier. Can the authors comment on this and report missingness and how this issue was handled in general?

6) What was the reason that the authors included stroke, MI and VF/VT in the composite variables. There is no right or wrong, but I think an explanation of this rational would help the reader understand. It is likely that by themselves these outcomes were to infrequent to allow for appropriate modeling, but one could ask why not other cardiovascular complications were also included.

7) The authors should be lauded for using sophisticated methodological, including sensitivity analyses and methods to reduce the chance of residual cofounding.

8) Looking at the tables, it becomes obvious that the presence of cardiovascular diseases are amongst the variables with the highest OR for adverse outcomes (higher than that for blood transfusions). Again this puts into question if it is not really the underlying disease that prompts clinicians to be more liberal in their transfusion practice to keep Hgb levels higher and ultimately drives the morbidity aspect. Would calculating attributable risk be of benefit? Of course this would also be limited but could shed some more light on this issue.

9) Although the authors attempted to control for procedure type in their analysis, it must be noted that within those categories major differences determining morbidity may exist. For example spine surgery can span the spectrum between laminectomies to extensive scoliosis correction surgery with massive blood loss.

Additional Questions:
Please enter your name: Stavros Memtsoudis

Job Title: Clinical Professor of Anesthesiology and Public Health/ Senior Scientist

Institution: Cornell/ HSS

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No
The authors report a retrospective cohort study on the association between perioperative transfusion of packed red blood cells (pRBC) and stroke or myocardial infarction (MI). Using data from a voluntary healthcare benchmarking database capturing approximately 20% of U.S. hospitalizations, the authors used time-stamped lab/procedure claims and ICD-9-CM diagnosis codes to ascertain pRBC transfusion and the outcomes of interest. They found a substantial association between pRBC transfusion and the risk of stroke and MI. This is a very well-written manuscript detailing a thoughtful analysis on an important clinical topic. Below are a few specific comments that may help to improve this paper.

Specific comments:

1. Page 7, line 9 states that a subgroup analysis was performed limited to patients who did not receive transfusion on postoperative days 1-7, but on page Page 5, line 15 it states that all patients undergoing transfusion on postoperative days 2-7 were excluded. Could the authors please clarify this? Do they simply mean that the primary analysis excluded those transfused from day 2-7, and the subgroup analysis additionally excluded those transfused on postoperative day 1? Also, what about patients with transfusion beyond postoperative day 7?? I realize this would be rare, but it would be helpful to clarify.

2. The statistical approach is nicely done and very clearly explained. I just have a few questions:
   a. Why not model the number of pRBCs as a continuous variable? In our paper (reference 2 in your paper), besides the primary finding of increased stroke/MI risk with hemorrhage requiring >4 units of pRBCs, in a secondary analysis we found a nicely linear relationship between the overall number of pRBCs transfused and the risk of stroke/MI.
   b. Why meqrlogit instead of xtmelogit?

3. Page 10, line 49: Just to be completely correct, would add something like “Although not perfectly population-representative, these findings …”

4. The inclusion of VT/VF in the composite outcome distracts from the overall message of the paper. At the very least, there should be an explanation of the rationale for including it, and it should be more consistently referred to (e.g., the the Results of the Abstract refer only to stroke/MI, as does Table 4). I would favor removing VT/VF altogether, or including it as a secondary outcome.

5. I agree with the authors that a substantial portion of the association between transfusion and stroke/MI is likely to be causal. But it should be acknowledged that it is not possible to completely tease apart the deleterious effect of transfusion from the deleterious effect of bleeding. Even a single-unit transfusion may reflect surgical oozing that may activate innate hemostatic mechanisms. The data cited on transfusion after PCI is compelling, but it is not in a directly comparable population since one would expect generally more blood loss with surgery than with PCI. I think it would make the paper stronger to mention this in the limitations section.

6. Conclusion: I think it is fine to call for more randomized trials, but given existing randomized trial results (refs 18 and 19), I think a somewhat stronger claim for transfusion-sparing strategies can be made. Something to the effect of, “Our findings of rare but serious adverse outcomes, combined with several randomized trials showing the safety of transfusion-sparing approaches in critical care and postoperative medicine, argue for …”

Additional Questions:

Please enter your name: Hooman Kamel

Job Title: Assistant Professor

Institution: Weill Cornell Medical College

Reimbursement for attending a symposium?: No
Reviewer: 3

Recommendation:

Comments:
The authors have performed a thoughtful and detailed analysis of an important question -- does discretionary day-of-surgery transfusion have an impact. By excluding patients that receive 5+ units over the hospital admission, or receive PRBCs on later postoperative days, the impact of procedure-related anemia transfusion is more clearly identified.

Methods
- there is a multitude of testing performed. most of it appears to have been predefined. was a protocol submitted or registered that documents the various and many subgroup and sensitivity analyses
- it is unclear to me whether all documented discharge diagnoses were available for the elixhauser comorbidity scoring -- how many diagnoses were the min/max/median?. the methods suggest primary and secondary were used. unclear if secondary includes comorbidity codes as opposed to pure "secondary" codes
- why is the non-mixed model logistic regression presented or used at all? we know that there is clustering of patients at the hospital level and that fixed hospital covariates do not incorporate all of the unmeasured hospital-level effects. The authors are to be commended for using a mixed effects model, but I would recommend for simplicity and readability, that the mixed effects model, with hospital as a random effect, is the primary analyses presented. although it is described as the "primary logistic regression model", the methods section seems to describe a very iterative process where different pieces are added/removed. I presume the authors did not retain variables that were predictors in the standard model but eliminated in the mixed effects. However, the "manual iterative forward technique" leaves it unclear if the same thresholds are applied through all phases (fixed and mixed)
- correct "compliment" to "complement"
- the propensity score analysis is concerning given how poor the ROC for that regression is.

Results
- the term "packed red blood cells" should not be introduced in the results section. either use pRBC throughout, or stay with RBC. it makes the reader wonder
- the obesity % in table 1 seem very underreported. is this purely ICD9 data, or are actual BMIs used?
- is table 2 the mixed effects model results, or standard fixed effects logistic regression only?
- I think univariate odds ratios are not helpful in table 2 and make it harder to read. thank you for the transparency, but it comes at the expense of readability
- table 2: by orthopedic, you mean joint replacement, correct?
- the title of the paper and the data presented are inconsistent. the title is regarding "single unit" while patients up to 4 units are included. maybe discretionary transfusion is a better title?

Discussion
- I think the discussion is divergent from the actual data presented and their unique value. instead of summarizing the known literature, I think the authors should be more focused on their data: that even 1 unit of PRBC confers risk. the dose dependent relationship they have demonstrated is also impressive. The authors should focus on the "discretionary" transfusions aspect of their data.
- other limitations include the absence of hemodynamic data. it remains unclear whether the alternatives to transfusion (crystalloid?) are preferable. the absence of any clinical data prevents us from knowing that the patients had similar hemodynamic profiles prior to transfusion
Additional Questions:
Please enter your name: Sachin Kheterpal

Job Title: Associate Professor of Anesthesiology

Institution: University of Michigan

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: None. Sponsored research funds paid to our department are in an unrelated clinical subject.

END

Date Sent:
26-Mar-2015