Reviewer's report

Title: Association between red blood cell storage duration and clinical outcome in patients undergoing off-pump coronary artery bypass surgery: A retrospective study

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Reviewer: Yasuko Nagasaka

Reviewer's report:

The current article by Jeong Jin Min et al. highlights the pitfalls of stored blood transfusion. Despite of this study being retrospective, the authors elegantly present the risks of stored blood that increases wound infection, negative base excess and longer hospitalization.

Here are my comments that may help improve this article.

Major Compulsory Revisions:

A. Overall comments

1. Unclear rationale: The use of off-pump CABG vs. on-pump significantly reduced risk of blood transfusion (50.7% vs. 63.3%, relative risk 0.80, CI 0.75-0.85, p<0.001) (Ref 1).

Since the patient population already has reduced risk for blood transfusion, please specify why this study is important.

2. Overlapping endpoints and contradiction:

   (Primary endpoints)

   a. Four primary endpoints (death from cardiac causes, myocardial infarction, coronary revascularization and stroke) have been studied. I see the first three points are cardiac; which include death from cardiac causes, MI, coronary revascularization. I wonder what exactly was the diagnosis of cardiac death in each patient.

   b. Did death from cardiac causes include low cardiac output, ventricular tachycardia, ventricular fibrillation or other fatal arrhythmias? How many of them required immediate intervention, IABP or re-open heart surgery. Please describe in detail.

   c. What is the definition of MI? What are the troponin levels in each patient? Are the MIs all STEMI? What are the results from TTE/TEE, radionuclear imaging or electrophysiological studies? What other treatments? Did they receive anything besides of revascularization?

   d. Are stroke hemorrhagic or thromboembolic stroke?

Did you see any association between each stroke and old blood transfusion?

What were the outcomes of stroke and did they correlate with old blood
transfusion?

(Other endpoints)

a. The authors have defined respiratory complications as ‘postoperative pneumonia or over 48 hrs of ventilatory support’. However, ‘prolonged intubation’ is listed as a separate endpoint in a different section. Typically prolonged intubation is defined as ‘longer than 48 hours’ (Ref 2) and is identical to the former endpoint. Please describe in details.

b. What are the inclusion criteria for the postoperative pneumonia?

c. Postoperative wound complication and mediastinitis may co-exist. However, the authors listed as separate endpoints at the beginning. Nevertheless, both were included in later paragraph: ‘superficial and deep sternal wound including mediastinitis’. It is very confusing.

These contradictions need to be sorted out.

It may also be helpful if you could utilize the scoring system to summarize the severity of your postoperative patients, i.e. SOFA, MODS, etc.

B. Major comments

1. Background

a. The authors state cell free hemoglobin decreases bioavailability of nitrous oxide. The two references (Ref 1 and 2) are written based upon the observations on nitric oxide. Same statement (nitrous oxide) is found in the discussion section as well. Please comment on this.

b. Several statements in the background are made without references. Please insert each reference that applies.

2. Methods

a. Results were adjusted for confounders (Table 3). What confounding factors did you adjust and how? Please explain in detail.

b. Unclear time frame. How did you define ‘long-term’ for the postoperative major adverse cardiovascular and cerebral events (MACCEs)?

c. Factors that affect outcome of cardiac events are not analyzed yet.

i. Preoperative medications (beta-blocker, statins, aspirin, metformin, ace inhibitors in patients with heart failure, etc)

ii. Intra and peri-operative factors (anesthesia methods i.e. volatile anesthetics vs. intravenous, hemodynamics i.e. lowest MAP and/or HR, lowest hemoglobin, events of cardiac arrest, etc)

iii. Postoperative factors (pain control, medications, etc).

3. Results and discussion

a. Please comment on the impacts of male dominancy on the outcome of this study (Table 1: 71.5% of the studied patients were male).

b. The sole positive result associated with old blood transfusion was wound
infection, which has already been reported previously. In the author’s institution leukoreduction was not routinely performed. Recent study shows prestorage leukoreduction reduces bacterial contaminations (Ref 3). Please comment on this.

c. Was there any other infections? Please state presence/absence of other infections, i.e. urinary tract infection, cavitary abscess, empyema, blood culture positive bacteremia, etc. What are the results from microbiology or radiology?

d. Long-term MACCEs: The authors have included prevalence of MACCE= 181 patients. If we add the numbers of patients, i.e. 15 deaths from cardiac causes, 48 MIs, 88 coronary revascularizations, 44 strokes = 195 patients. Please comment on the overlapping numbers of patients.

e. In the discussion the authors state tissue hypoperfusion predisposes wound infection: ‘transfusion-related immunomodulation in the blood recipients, …, and the persistent inflammation at the wound site due to reduced bioavailability of nitrous oxide’.

Please comment if this is about nitric oxide (NO).

Is there any literature that suggests reduced NO availability triggers wound infection?

f. Did you look at the indicators for hemolysis in patients received old/new blood? i.e. haptoglobin, plasma Hb level, bilirubin, or Hb level after transfusion?

Minor Essential Revisions:
The native English speaker should correct grammatical errors.

References:


Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests.