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Randomized trial of red cell washing for the prevention of transfusion-associated organ injury in cardiac surgery

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Abstract

Background. Experimental studies suggest that mechanical cell washing to remove pro-inflammatory components that accumulate in the supernatant of stored donor red blood cells (RBCs) might reduce inflammation and organ injury in transfused patients.

Methods. Cardiac surgery patients at increased risk of large-volume RBC transfusion were eligible. Participants were randomized to receive either mechanically washed allogenic RBCs or standard care RBCs. The primary outcome was serum interleukin-8 measured at baseline and at four postsurgery time points. A mechanism substudy evaluated the effects of washing on stored RBCs *in vitro* and on markers of platelet, leucocyte, and endothelial activation in trial subjects.

Results. Sixty adult cardiac surgery patients at three UK cardiac centres were enrolled between September 2013 and March 2015. Subjects received a median of 3.5 (interquartile range 2–5.5) RBC units, stored for a mean of 21 (SD 5.2) days, within 48 h of surgery. Mechanical washing reduced concentrations of RBC-derived microvesicles but increased cell-free haemoglobin concentrations in RBC supernatant relative to standard care RBC supernatant. There was no difference between groups with respect to perioperative serum interleukin-8 values [adjusted mean difference 0.239 (95% confidence intervals −0.231, 0.709), $P=0.318$] or concentrations of plasma RBC microvesicles, platelet and leucocyte activation, plasma cell-free haemoglobin, endothelial activation, or biomarkers of heart, lung, or kidney injury.

Conclusions. These results do not support a hypothesis that allogenic red blood cell washing has clinical benefits in cardiac surgery.

Clinical trial registration. ISRCTN 27076315.

Key words: Cardiovascular surgery; inflammation; transfusion

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Editor's key points

- Experimental evidence supports a benefit to red blood cell (RBC) washing to reduce inflammatory factors before transfusion.
- In a randomized trial of washed and standard unwashed RBCs in high-risk cardiac surgery patients, the experimental benefit was not replicated.
- Owing to the limited power of this trial, larger studies are necessary to test the hypothesis that RBC washing is beneficial.

Organ injury associated with red blood cell (RBC) transfusion has been attributed to a 'storage lesion'; a progressive disruption of erythrocyte homeostasis associated with depletion of high-energy phosphates during storage that results in accumulation of microparticles and other inflammatory substances in the supernatant of RBCs.[1] Experimental studies implicate platelet and monocyte activation by RBC microparticles, and endothelial dysfunction as a consequence of altered haem metabolism, in transfusion-associated organ injury,[2–5] and suggest that removal of the storage supernatant by cell washing attenuates inflammatory responses and organ dysfunction.[2 6] In support of these findings, washing of allogeneic RBCs has been shown to attenuate inflammation in children undergoing cardiac surgery.[7] We tested the hypothesis that allogeneic RBC washing attenuates inflammation and organ failure in adult cardiac surgery patients receiving large-volume transfusions. In a prespecified substudy, we tested the hypothesis that RBC washing attenuates platelet and leucocyte activation by removing inflammatory RBC microparticles. We also assessed whether cell-free haemoglobin (Hgb) release by RBCs after washing results in endothelial activation.

Methods

The Red Cell Washing for the Attenuation of Organ Injury Following Cardiac Surgery (REDWASH) trial was a multicentre, single-blinded, parallel-group, randomized controlled trial of washing of allogeneic RBCs before transfusion *vs* standard care (no washing). The trial had ethical approval (REC Reference 12/EM/0475) and was registered (ISRCTN 27076315). The trial protocol has been published;[8] changes to the study design after trial commencement are listed in the online Supplementary material. The main trial was terminated by the funder in March 2015 because of slow recruitment. This report includes the results of a prespecified mechanistic substudy planned for the first 60 patients recruited.[8] A detailed description of the study methods is available as online Supplementary material.

Patients

Adults (≥16 yr of age) undergoing cardiac surgery with blood cardioplegia identified as representing a high-risk group for large-volume blood transfusion (LVBT) using a modified risk score[9] (score ≥25) were eligible for inclusion. Exclusion criteria are listed in Supplementary Table S1.

Randomization and blinding

Subjects were randomly assigned with concealed allocation using an Internet-based randomization system (Sealed Envelope Ltd, Medicines Healthcare Regulatory Authority (MHRA) recognized facility). Randomization was stratified by study site and type of procedure. Outcome assessors were blinded to allocation.

Intervention

Eligible subjects who consented to participate were randomly allocated, in a 1:1 ratio, to receive either standard care (unwashed prestorage leucodepleted allogenic red blood cells) or washed red blood cells, between the commencement of surgery and 48 h after surgery. Allogeneic saline–adenine–glucose–mannitol (SAGM) stored RBC units used in the trial were issued by National Health Service Blood and Transplant (NHSBT) as per standard care. The Continuous AutoTransfusion System (CATS™; Fresenius AG, Bad Homburg, Germany) was used on the basis that low ***g*** force centrifugation with this device minimizes RBC trauma.[10 11] For the intervention, RBCs were washed in theatre or at the patient's bedside with saline using the Quality Mode and immediately administered to the patient. Washed units were not stored for future use. The haematocrit threshold for transfusion was 23. A major protocol violation was defined as receipt of only unwashed blood for subjects randomized to receive washed RBCs, or the receipt of only washed blood in patients randomized to receive standard care.

Outcomes

The primary outcome was severity of the systemic inflammatory response as indicated by serum interleukin (IL)-8 measured at baseline and at four postsurgery time points. We have previously shown that IL-8 is increased in transfused patients.[8 12] Secondary outcomes are described in Supplementary Table S2. For the mechanism study, serum, platelet-poor plasma, and urine samples were collected at baseline and a serial time points. Microparticles in storage supernatant and platelet-poor plasma were characterized using flow cytometry (Cyan ADP; Beckman Coulter, Brea, CA USA). Cell-free Hgb and plasma total and non-transferrin-bound iron were measured in the supernatant of RBC units and in plasma as described.[13–15] Platelet activation [platelet activating complex (PAC)-1 (BD Biosciences, Abingdon, Oxford, UK), P selectin/CD62P (Abcam, Cambridge, UK), and PE-coupled CD41 (Affymetrix, Santa Clara, CA, USA)] and leucocyte activation markers (CD64, CD163; Affymetrix) were measured using flow cytometry (Cyan ADP; Beckman Coulter) in whole blood. Platelet activation was also measured indirectly in whole blood using Multiplate aggregometry (Roche Diagnostics International Ltd, Rotkreuz, Switzerland). Serum bilirubin was measured on the Siemens Advia 2400 Chemistry System (Siemens, Frimley, UK). Hepcidin was measured using an enzyme-linked immunosorbent assay (Abbexa, Cambridge, UK). Serum intercellular adhesion molecule (ICAM)-1 was measured using multiplex assays on the MAGPIX (Luminex Corporation, Austin, TX, USA). Reactive oxygen species concentrations, protein carbonyl content, and thiobutiric acid reactive substances (TBARS) were measured with the following commercially available kits: OxiSelect (Cell Biolabs, Inc., San Diego, CA, USA), Parameter TBARS assay (R&D Systems, Abingdon, Oxford, UK), and carbonyl content assay kit (Abcam).

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