Prolonged storage of packed red blood cells for blood transfusion (Review)

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[Intervention Review]

Prolonged storage of packed red blood cells for blood transfusion

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ABSTRACT

Background

A blood transfusion is an acute intervention, used to address life- and health-threatening conditions on a short-term basis. Packed red blood cells are most often used for blood transfusion. Sometimes blood is transfused after prolonged storage but there is continuing debate as to whether transfusion of 'older' blood is as beneficial as transfusion of 'fresher' blood.

Objectives

To assess the clinical benefits and harms of prolonged storage of packed red blood cells, in comparison with fresh, on recipients of blood transfusion.

Search methods

We ran the search on 1st May 2014. We searched the Cochrane Injuries Group Specialized Register, Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*), MEDLINE (OvidSP), Embase (OvidSP), CINAHL (EBSCO Host) and two other databases. We also searched clinical trials registers and screened reference lists of the retrieved publications and reviews. We updated this search in June 2015 but these results have not yet been incorporated.

Selection criteria

Randomised clinical trials including participants assessed as requiring red blood cell transfusion were eligible for inclusion. Prolonged storage was defined as red blood cells stored for $\geq$ 21 days in a blood bank. We did not apply limits regarding the duration of follow-up, or country where the study took place. We excluded trials where patients received a combination of short- and long-stored blood products, and also trials without a clear definition of prolonged storage.

Data collection and analysis

We independently performed study selection, risk of bias assessment and data extraction by at least two review authors. The major outcomes were death from any cause, transfusion-related acute lung injury, and adverse events. We estimated relative risk for dichotomous outcomes. We measured statistical heterogeneity using I^2. We used a random-effects model to synthesise the findings.

Main results

We identified three randomised clinical trials, involving a total of 120 participants, comparing packed red blood cells with ≥ 21 days storage ('prolonged' or 'older') versus packed red blood cells with < 21 days storage ('fresh'). We pooled data to assess the effect of prolonged storage on death from any cause. The confidence in the results from these trials was very low, due to the bias in their design and their limited sample sizes.

The estimated effect of packed red blood cells with ≥ 21 days storage versus packed red blood cells with < 21 days storage for the outcome death from any cause was imprecise (5/45 [11.11%] versus 2/46 [4.34%]; RR 2.36; 95% CI 0.65 to 8.52; I^2: 0%, P = 0.26, very low quality of evidence). Trial sequential analysis, with only two trials, shows that we do not yet have convincing evidence that older packed red blood cells induce a 20% relative risk reduction of death from any cause compared with fresher packed red blood cells. No trial included other outcomes of interest specified in this review, namely transfusion-related acute lung injury, postoperative infections, and adverse events. The safety profile is unknown.

Authors' conclusions

Recognising the limitations of the review, relating to the size and nature of the included trials, this Cochrane Review provides no evidence to support or reject the use of packed red blood cells for blood transfusion which have been stored for ≥ 21 days ('prolonged' or 'older') compared with those stored for < 21 days ('fresh'). These results are based on three small single centre trials with high risks of bias. There is insufficient evidence to determine the effects of fresh or older packed red blood cells for blood transfusion. Therefore, we urge readers to interpret the trial results with caution. The results from four large ongoing trials will help to inform future updates of this review.

PLAIN LANGUAGE SUMMARY

Prolonged storage of packed red blood cells (storage of 21 days or more) in comparison with fresh cells on recipients of blood transfusion

Review question

We reviewed the clinical benefits and harms of prolonged storage of packed red blood cells (storage of 21 days or more) in comparison with the use of fresher packed red blood cells on recipients of blood transfusion.

Background

Blood transfusion is used to try to solve life- and health-threatening conditions on a short-term basis. Packed red blood cells are most often used for blood transfusion. Sometimes blood is transfused after prolonged storage of these cells but there is continuing debate as to whether transfusion of 'older' blood is as beneficial as transfusion of 'fresher' blood.

Study characteristics

We identified three studies, involving a total of 120 participants, comparing packed red blood cells stored for ≥ 21 days versus < 21 days.

Key results

The results of the studies for the outcome death from any cause were uncertain due to the small number of participants who contributed information. We could not exclude an effect on death with either longer or shorter storage. None of the trials considered the other outcomes of interest in this review, namely transfusion-related acute lung injury, postoperative infections, and adverse events. The safety profiles of the two approaches are unknown.

Quality of evidence

The level of confidence in the results of this review is very low. The studies have limitations in the way they were designed and executed. Moreover, the limited number of people included in the studies led to imprecise results. We are aware of four large ongoing trials in this area which will help us to better understand the effects of storage on red blood cells in relation to outcomes for patients.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Long-stored (older) PRBC (≥ 21 days of storage) compared with short-stored (fresh) PRBC (<21 days of storage) for patients requiring blood transfusion

Patient or population: patients requiring blood transfusion (children with malaria and adults with a traumatic injury)
Settings: intensive care unit
Intervention: Long-stored (older) PRBC (≥ 21 days of storage)
Comparison: Short-stored (fresh) PRBC (<21 days of storage)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Short-stored (fresh) PRBC (<21 days of storage)	Long-stored ('older') PRBC (≥ 21 days of storage)				
Death from any cause	**Study population**		**RR 2.36** (0.65 to 8.52)	91 (2 studies)	⊕◯◯◯ **very low**[1]	Dhabangi 2013 (children with malaria) Schulman 2002 (adults with a traumatic injury)
	43 per 1000	**103 per 1000** (28 to 370)				
	Low					
	43 per 1000	**101 per 1000** (28 to 366)				
Transfusion-related acute lung injury - not measured	See comment	See comment	Not estimable	-	See comment	No trial assessed this outcome.
Postoperative infections - not measured	See comment	See comment	Not estimable	-	See comment	No trial assessed this outcome.
Post-injury coagulopathy - not measured	See comment	See comment	Not estimable	-	See comment	No trial assessed this outcome.

Multiple organ failure post-injury - not measured	See comment	See comment	Not estimable	-	See comment	No trial assessed this outcome.
Adverse event (Hyperkalaemia) - not measured	See comment	See comment	Not estimable	-	See comment	No trial assessed this outcome.
Adverse event (Metabolic acidosis) Follow-up: 12 months	See comment	See comment	Not estimable	22 (1 study)	⊕◯◯◯ **very low**[2,3]	‘ ‘ No acid-base parameter changed significantly between the pre- and posttransfusion periods either within each group or comparing changes between the groups” (Walsh 2004).

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Small sample size and low event rate (91 participants with 7 events).
[2] The one trial had high risk of bias.
[3] Small sample size (22 participants) and no reported event rate of this outcome.

BACKGROUND

Transfusion of blood is the process of transferring blood cells from one person into the circulatory system of another (Sullivan 2007; Giangrande 2000). It is a very common procedure for a number of acute and chronic conditions. A blood transfusion is a costly intervention, implemented to solve life- and health-threatening conditions, and in general its long-term effects tend to be of secondary importance (Tsai 2010). This potentially life-saving intervention is, however, associated with adverse events, categorised as immune or non-immune hazards (Hendrickson 2009) (Appendix 1). Formerly, whole blood was transfused. During the last 30 years, packed red blood cells have been most often used for blood transfusion. Packed red blood cells were introduced to reduce the immunisation hazards of whole blood and to preserve leucocyte-rich and thrombocyte-rich blood products for more targeted use for people lacking these components.

Many clinical studies have suggested a general association between transfusion and morbidity (Dunne 2004; Leal-Noval 2001; Leal-Noval 2003; Malone 2003; Mynster 2000; Vamvakas 1999; Vamvakas 2002; Vamvakas 2006) and mortality (Ho 2003; Robinson 2005; Spinella 2009). One critical question that needs to be answered is, "Are the short- and long-term effects of blood transfusion intrinsic to the process or are they exaggerated by *blood storage*?" (Tsai 2010). However, specific concern has been expressed as to whether use of blood transfusion may contribute to adverse outcomes in people receiving transfusions, because of a cellular and biochemical phenomenon called the '*storage lesion*' of red cells (Bosman 2008; Lelubre 2009; Tinmouth 2006; Zimrin 2009). This is a very controversial issue in clinical medicine (Zimring 2013).

What is blood storage?

All blood transfusion services store collected red blood cells in a specific additive medium, which includes anti-coagulants and nutrients. Most current red blood cell storage solutions are composed of dextrose, phosphate, adenine, and citrate (Hess 2006). Use of these solutions allows units (or bags) of red blood cells to be stored for a period of time prior to transfusion at 2ºC to 6ºC in blood banks, which considerably facilitates inventory management at national, regional, and hospital levels. The development of blood storage systems has allowed donation and transfusion to be separated in time and space (Zimrin 2009).

Peyton Rous was the first person to store red blood cells (Zimrin 2009). In 1915, Rous and Turner developed the first red blood cell storage solution, a mixture of citrate and glucose, for storing rabbit red blood cells for use in a heterophil agglutination test for syphilis (Hess 2006). Historically, the shelf-life of red blood cells was established based on biochemical standards and survival studies, conducted largely in healthy volunteers and not in patients. The typical recovery of red blood cells post transfusion was 75% to 89% and the percentage of haemolysis was 0.1% to 0.4% (Hess 2006).

An extensive review of the history of red blood cell storage solution has been published (Hess 2006). For details of red blood cell storage solutions and a glossary, see Appendix 2 and Appendix 3, respectively.

Definition of red blood cell storage lesion

Red blood cell storage lesion is the name given to all of the biochemical and biomechanical changes that occur within the red blood cell and the supernatant (including plasma and the storage media) during conventional blood bank storage (Hess 2010; Hess 2010a). During storage, red blood cells lose potassium, diphosphoglycerate, adenosine 5′-triphosphate (ATP), lipids and membranes, while becoming more rigid and demonstrating reduced oxygen off-loading. Stored units become more acidotic and the suspending fluid has higher concentrations of free haemoglobin and biologically-active lipids, and contains greater quantities of negatively-charged microvesicles with pro-inflammatory and procoagulant activity (Hess 2006). The components of the red blood cell storage lesion are metabolic, enzymatic, oxidative, and physiologic (Hess 2010; Hess 2010a). This results in changes in red blood cell metabolism, shape, and rheology; loss of membrane carbohydrates, lipids and proteins; and alterations in secretion, oxygen delivery, and adhesion (Hess 2010a). Details of these changes are shown in Appendix 4.

Definition of prolonged storage

There is no consensus on the duration of storage that is considered to be 'prolonged' (Flegel 2014; Triulzi 2010). Donated red blood cells can be stored for as long as 42 days at 2ºC to 6ºC (Hebert 2005; Yap 2008). Duration of storage has been described as "the number of calendar days between the day of collection of the red blood cell unit and the day of transfusion" (Gauvin 2010). However, there is no consensus on what is meant by prolonged storage or 'older' red blood cells. Data from observational clinical studies reporting transfusion of 'older' red blood cells describe a wide range from 14 days to 24 days (Zimrin 2009). The data from an extensive narrative review of randomised controlled trials of the transfusion of 'older' red blood cells report a wider range of 5 to 20 days (Zimrin 2009).

Storage and trauma patients

Haemorrhagic shock is the second most frequent cause of death in trauma patients (Tien 2007). It has been shown to be responsible for 30% to 40% of trauma mortalities (Theusinger 2009). Several observational studies have been conducted in critical care and intensive care unit patients to assess the impact of red blood cell stor-

age (Keller 2002; Leal-Noval 2008; Murrell 2005; Offner 2002; Spinella 2009; Wienberg 2008b; Zallen 1999). The transfusion of blood and its components is critical in the management of traumatic haemorrhage and other conditions, but is itself associated with adverse outcomes (Greer 2010; Theusinger 2009). Some of the clinical consequences associated with the transfusion of 'older' packed red cells include multi-organ failure (Spinella 2009; Zallen 1999), infections (Offner 2002), mortality (Purdy 1997; Spinella 2009; Weinberg 2008a; Wienberg 2008b), renal failure (Wienberg 2008b), pneumonia (Vandromme 2009; Wienberg 2008b), and deep vein thrombosis (Spinella 2009). Recently, a retrospective study reported red blood cell storage is not associated with an increasing risk of death in critically ill people (Aubron 2014).

Storage and non-trauma patients

Serious complications and mortality after cardiac surgery have been associated with the prolonged storage of transfused red cells (Basran 2006; Koch 2008; Leal-Noval 2003; Vamvakas 2000; Watering 2006; Yap 2008).

Gauvin 2010 described an association between the length of storage of transfused red blood cells and multiple organ dysfunction syndrome in paediatric intensive care patients.

Studies of red blood cell storage in colorectal and biliary surgery have reported an increase in the risk of postoperative infections (Edna 1994; Edna 1998; Mynster 2000; Mynster 2001).

Potential adverse events induced by storage

Transfusion of red blood cells after prolonged storage may produce harmful effects that could be mediated by several pathways (Hod 2010). The following storage-induced potential adverse events have been both suggested and reported, which may underlie why patients receiving 'older' blood have a longer stay in intensive care units (Murrell 2005).

1. Cardiac arrhythmia induced by hyperkalaemia (Hess 2010).
2. Transfusion-related acute lung injury due to the alteration of erythrocyte phospholipids and generation of platelet activating factor (Hess 2010; Goldberg 2012).
3. Reduction in the efficacy of transfused blood components by reducing their flow, functional capacity, and survival (Hess 2010a).
4. Contaminating bacteria and infection (Hess 2010a; Hod 2011).
5. Immunosuppression (Purdy 1997).
6. Multiple organ failure post-injury (Gauvin 2010; Offner 2002).
7. Reduction of cerebral oxygenation in patients with severe traumatic brain injury (Leal-Noval 2008).
8. Post-injury coagulopathy (Maani 2009).
9. Thrombosis (Sweeney 2009; Zimrin 2009) and adverse effects on global coagulation status (Aucar 2009; Bosman 2008).
10. Immune haemolytic transfusion reaction (Zimrin 2009).
11. Postoperative infections risk (Edna 1994; Edna 1998).

See Appendix 3 for glossary.

Why it is important to do this review

This Cochrane Review was conducted for the following reasons:

- *First,* it has been difficult to establish whether there are significant clinical implications in transfusing red blood cells after prolonged storage (Hess 2010a; Qu 2015; Sparrow 2015; Van De Watering 2013). There is an active debate on whether transfusion of 'older' blood is as beneficial as transfusion of 'fresher' blood (Glynn 2010). An association between the duration of storage of transfused red blood cells and morbidity and mortality in adult patients is considered by some to be an established fact but by others to be a myth (Almac 2007; Lelubre 2009). In one opinion in cardiac surgery, transfusion of 'older' blood is inherently more fraught with complications and poorer outcomes (Koch 2008). However, Yap 2008 reported that the age of transfused red cells is not associated with early mortality and morbidity after cardiac surgery.

- *Second*, there is uncertainty as to the true clinical impact of prolonged storage of red blood cells on microcirculation and tissue oxygenation in critically ill patients (Frenzel 2009).

- *Third*, observational clinical studies (prospective and retrospective) are the source of most of our knowledge on "the importance of the question of whether or not storage of red blood cell affects clinical outcomes" (Stowell 2010). However, such studies with observational design are not able to correctly assess the benefits and harms of intervention (Deeks 2003; Jakobsen 2013).

- *Fourth*, patients receiving 'older' blood seem to have a significantly longer stay in intensive care units (Murrell 2005).

- *Fifth*, there is a need to assess the methodological quality of randomised clinical trials on the duration of storage of red blood cells for transfusion in a variety of clinical settings (Bennett-Guerrero 2009; Hebert 2005; Schulman 2002).

- *Sixth*, a recent meta-analysis on "the purported deleterious effects of 'old' (versus 'fresh') red blood cells did not report the risk of bias of the included randomised clinical trials, did not use the I^2 statistic to quantify the statistical heterogeneity, did not consider risks of random error with current methodology (Brok 2008; Brok 2009; Thorlund 2011; Wetterslev 2008; Wetterslev 2009) and was conducted by just one author. All of these factors may have led to bias (Vamvakas 2010).

OBJECTIVES

To assess the effects of prolonged compared with shorter storage of packed red blood cells for red blood cell transfusion.

The focus is packed red blood cells, as they are the most frequently transfused blood product. For this review, prolonged storage is defined as storage of 21 days or more. We chose this threshold since it is the chronological midpoint in storage duration for additive solution units (42 days) (Bennett-Guerrero 2009).

METHODS

Criteria for considering studies for this review

Types of studies

All randomised clinical trials, irrespective of publication status (trials might be unpublished or published as an article, an abstract or a letter), language of publication, country where the study took place, or period of follow-up. We included randomised clinical trials conducted in a hospital or community setting or both. We did not apply any limits with respect to the period of follow-up. We excluded randomised clinical trials conducted without definition of the term 'prolonged storage', or where the definition was unclear.

Types of participants

Any participant requiring a red blood cell transfusion. No limitation was applied on the age of participants.
We included randomised clinical trials in which participants received either only long-stored or only short-stored blood products. We excluded randomised clinical trials where patients received a combination of short- and long-stored blood products.

Types of interventions

Intervention

- Red blood cells stored for ≥ 21 days in a blood bank.

Comparison

- Red blood cells stored for < 21 days in a blood bank.

Types of outcome measures

Primary outcomes

Clinical effectiveness outcomes

1. Death from any cause.
2. Transfusion-related acute lung injury.
3. Adverse events: number and type of adverse events defined as patients with any untoward medical occurrence not necessarily having a causal relationship with the treatment. We reported on adverse events that lead to treatment discontinuation and those that have not lead to treatment discontinuation separately. We have defined serious adverse events according to the International Conference on Harmonisation (ICH) Guidelines (ICH-GCP 1997) as any event that at any dose results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability, or is a congenital anomaly/birth defect, and any important medical event, which may have jeopardised the patient or requires intervention to prevent it. All other adverse events were considered non-serious.

Secondary outcomes

1. Postoperative infections.
2. Postinjury coagulopathy defined by arbitrary thresholds in standard laboratory parameters as follows: 1) prothrombin time more than 18 seconds; (2) activated partial thromboplastin time more than 60 seconds; (3) prothrombin time/activated partial thromboplastin time > 1.5 (1.6) control values; (4) international normalised ratio (INR) > 1.2 (prothrombin time); (5) international normalised ratio > 1.5 (prothrombin time); (6) quick value of more than 70% (prothrombin time) (Stahel 2009).
3. Multiple organ failure post-injury.

Safety outcomes

1. Hyperkalaemia.
2. Metabolic acidosis.

See Appendix 3 for definitions.

Search methods for identification of studies

In order to reduce publication and retrieval bias we did not restrict our search by language, date or publication status.

Electronic searches

The Cochrane Injuries Group Trials Search Co-ordinator searched the following:

1. Cochrane Injuries Group Specialised Register (10/05/2014);

2. Cochrane Central Register of Controlled Trials, *The Cochrane Library* (issue 4, 2014);
3. Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R) 1946 to 10/05/2014;
4. Embase Classic+Embase (OvidSP) 1947 to 10/05/2014;
5. CINAHL Plus (EBSCOHost) (1937 to 10/05/2014);
6. ISI Web of Science:Science Citation Index Expanded (SCI-EXPANDED) 1970 to 10/05/2014;
7. ISI Web of Science: Conference Proceedings Citation Index- Science (CPCI-S) 1990 to 10/05/2014;
8. LILACS (http://lilacs.bvsalud.org/) (10/05/2014);
9. Clinicaltrials.gov (www.clinicaltrials.gov) 10/05/2014;
10. WHO Clinical Trials Search Portal (http://apps.who.int/trialsearch/) (10/05/2014).

We adapted the MEDLINE search strategy illustrated in Appendix 5 as necessary for each of the other databases. We used search filters, a modified version of the 'Cochrane Highly Sensitive Search Strategies, for identifying randomized trials in MEDLINE and Embase (Lefebvre 2011).

We performed a further search in June 2015. Those results have been added to Studies awaiting classification and will be incorporated into the review at the next update.

Searching other resources

We also searched the following websites:

- Transfusion Evidence Library (http://transfusionguidelines.org);
- NHS Evidence (http://www.evidence.nhs.uk);
- American Association of Blood Banks (http://www.aabb.org).

In addition, we checked the reference lists of identified material for relevant trials.

Data collection and analysis

Selection of studies

Arturo Martí-Carvajal and Daniel Simancas independently assessed for inclusion all the potential studies identified by the search strategy. We contacted the authors of one trial (Dhabangi 2013), in order to clarify details in order to decide whether the trial should be included or excluded.

Data extraction and management

Arturo Martí-Carvajal, Barbra Peña-González and Daniel Simancas independently extracted data from the selected trials using a standardised data extraction form (Zavala 2006). We extracted the following data: eligibility criteria, demographics (age, gender, country), storage duration (days), reason for transfusion, setting of the patients (i.e. cardiac surgery, intensive care unit), outcomes. We did not contact any trial author regarding missing data, because there was no need to do so.

Assessment of risk of bias in included studies

Arturo Martí-Carvajal and Daniel Simancas independently assessed the quality of each trial using a simple form following the domain-based evaluation as described in the *Cochrane Handbook* (Higgins 2011). We compared the assessments and discussed any discrepancies between the review authors. We resolved disagreements through discussion and consensus.

The definitions of each classification are given below.

Generation of randomisation sequence (checking for possible selection bias)

- Low risk: any truly random process (e.g. random number table, computer random number generator).
- High risk: any non-random process (e.g. odd or even date of birth, hospital or clinic record number).
- Unclear: the trial was described as randomised but the method used for the allocation sequence generation was not described.

Allocation concealment (checking for possible selection bias)

- Low risk: e.g. telephone or central randomisation, consecutively numbered sealed opaque envelopes.
- High risk: open random allocation, unsealed or non-opaque envelopes, alternation, date of birth.
- Unclear: the trial was described as randomised but the method used to conceal the allocation was not described.

Blinding or masking (checking for possible performance bias)

- Low risk: participants, carers/personnel and/or outcome assessors blinded from the knowledge of which intervention the participant received, or the lack of blinding could not have affected the results;
- High risk: participants, carers/personnel and/or outcome assessors were not blinded from the knowledge of which intervention the participant received, and this could have affected the results;
- Unclear: the blinding of participants, carers/personnel and/or outcome assessors was not reported.

Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

- Low risk (any one of the following): no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention

effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on the observed effect size; missing data have been imputed using appropriate methods.

- High risk (any one of the following): reason for missing outcome data likely to be related to the true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in the observed effect size; 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
- Unclear risk (any one of the following): insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomised not stated, no reasons for missing data provided); the study did not address this outcome.

Selective reporting bias

- Low risk (any one of the following): the study protocol is available and all the pre-specified (primary and secondary) outcomes were reported in the final report, or the study protocol was not available but it was clear that the published reports included all expected outcomes.
- High risk (any one of the following): not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
- Unclear risk: insufficient information available to permit judgement of 'Low risk' or 'High risk'.

Other biases

We described for each included study any important concerns about other possible sources of bias (baseline imbalance, sponsorship bias, confirmation bias, bias of the presentation data, etc.)

- Low risk of bias: the trial appears to be free of other components that could put it at risk of bias;
- Unclear risk: the trial may or may not be free of other components that could put it at risk of bias;
- High risk of bias: there are other factors in the trial that could put it at risk of bias.

Measures of treatment effect

Binary data was available for death from any cause and measured using the risk ratio (RR) with 95% confidence intervals (CI).

Unit of analysis issues

The unit of analysis was the participant.

Dealing with missing data

We would have used the following procedures (and will apply these for future updates, if possible). We would have noted levels of attrition and explored the impact of high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes we would have carried out analysis, as far as possible, on an intention-to-treat basis (i.e. we would have attempted to include all participants randomised to each group in the analyses). The denominator for each outcome in each trial would have been the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We conducted a meta-analysis on death from any cause. We quantified statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across trials that is due to heterogeneity rather than sampling error (Higgins 2003). We considered there to be significant statistical heterogeneity if $I^2 > 75\%$ and moderate statistical heterogeneity if the I^2 was between 50 and 74% (Higgins 2011).

Assessment of reporting biases

Only three trials were available, so publication bias was not explored.

We would also have attempted to assess whether trials included in the review are affected by publication bias, by using a funnel plot to graphically illustrate variability between trials. If asymmetry were detected, we would have explored causes other than publication bias (e.g. selective outcome reporting, poor methodological quality in smaller studies, true heterogeneity) (Higgins 2011). In future updates we will construct a funnel plot, provided we have ten or more randomised clinical trials for each comparison (Sterne 2011).

Data synthesis

We carried out statistical analysis with Review Manager software (RevMan 2011) using the random-effects model.

Trial Sequential Analysis

Trial sequential analysis (TSA) was applied, as cumulative meta-analyses are at risk of producing random errors due to sparse data and repetitive testing of the accumulating data (Wetterslev 2008). To minimise random errors, we calculated the required information size (i.e., the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) (Thorlund 2009; Wetterslev 2008). The required information size calculation should also account for the heterogeneity or diversity present in the meta-analysis (Wetterslev 2008; Wetterslev 2009). We planned to conduct our meta-analysis using the following assumptions: the required information size would have been based on the event proportion in the control group; assumption of a plausible RR reduction of 20% on the RR reduction observed in the included trials with low risk of bias; a risk of type I error of 5%; a risk of type II error of 20%; and the assumed diversity of the meta-analysis (Wetterslev 2009). The underlying assumption of trial sequential analysis is that testing for significance may be performed each time a new trial is added to the meta-analysis. We added the trials according to the year of publication, and if more than one trial has been published in a year, trials were added alphabetically according to the last name of the first author. On the basis of the required information size, trial sequential monitoring boundaries were constructed (Thorlund 2011; Wetterslev 2008). These boundaries determine the statistical inference one may draw regarding the cumulative meta-analysis that has not reached the required information size; if the trial sequential alpha-spending monitoring boundary is crossed before the required information size is reached, firm evidence may perhaps be established and further trials may turn out to be superfluous. On the other hand, if the boundary is not surpassed, it is most probably necessary to continue doing trials in order to detect or reject a certain intervention effect. That can be determined by assessing if the cumulative Z-curve crosses the trial sequential beta-spending boundaries.
We conducted TSA for exploring the effect of the intervention on death from any cause.

Subgroup analysis and investigation of heterogeneity

Meta-analysis of two small trials involving 91 participants showed no important heterogeneity.
We would have used the following procedures (and will apply these for future updates, if possible). We had anticipated clinical heterogeneity in the effect of the intervention and we had proposed to conduct the following subgroup analyses.

1. Age
2. Type of storage duration definition
3. Medical versus surgical indications
4. By using arbitrary cut-off points of units transfused:
    - one unit
    - two units
    - three or more units

Sensitivity analysis

We would also have conducted sensitivity analysis according to the methods outlined in the *Cochrane Handbook* (Higgins 2011). In future updates, if sufficient trials are identified, we will conduct a sensitivity analysis comparing: trials with 'low risk of bias' versus those at 'high or unclear risk of bias' in the domain allocation concealment.

Summary of findings tables

We used GRADE (Guyatt 2011) to assess the quality of the body of evidence. The summary of findings was constructed using GRADEpro software (GRADEpro 2008). The GRADE approach appraises the quality of a body of evidence, based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence considers within-study risk of bias (methodological quality), the directness of the evidence, heterogeneity of the data, precision of effect estimates and risk of publication bias (Balshem 2011; Brozek 2011; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g).
Summary of findings for the main comparison shows the body of evidence for the outcomes reported by the included trials i.e., death from any cause and metabolic acidosis. However, we included other unreported outcomes to show the lack of evidence.
We would have used (and will apply in future updates, if possible) the principles of the GRADE system to assess the quality of the body of evidence associated with other outcomes of interest to this review.

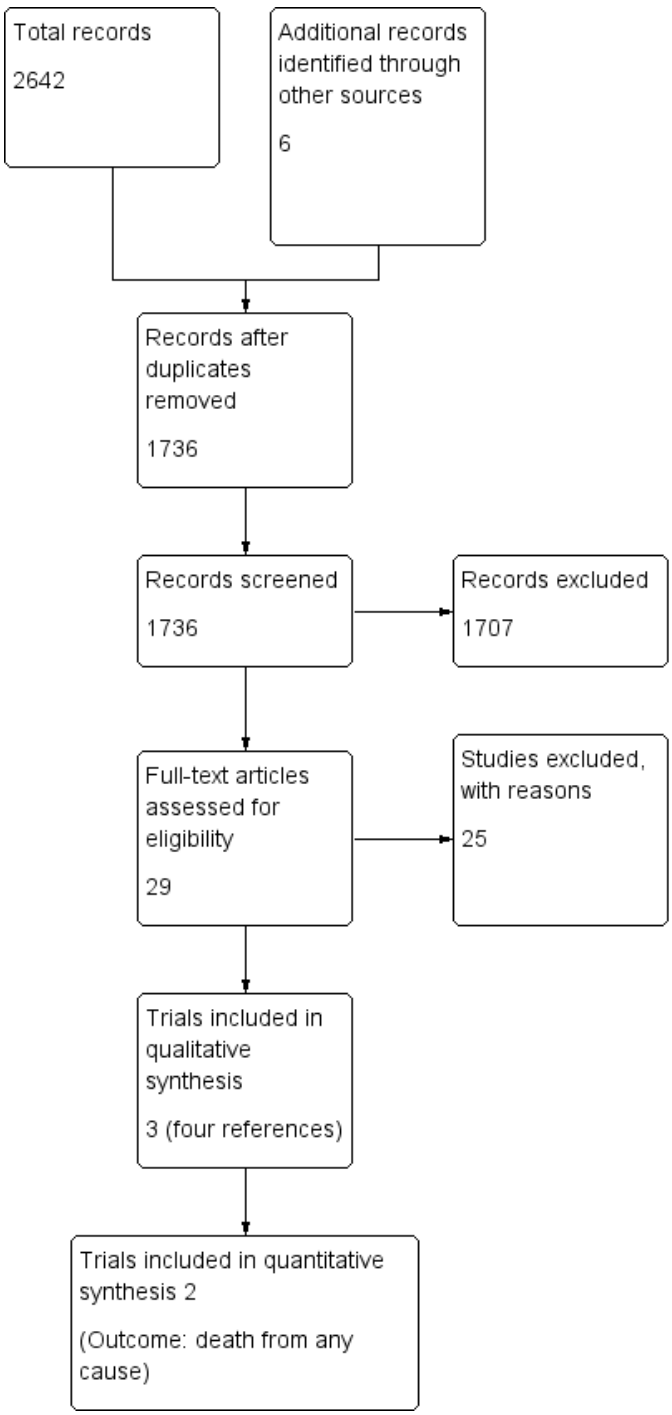
RESULTS

Description of studies

Results of the search

We identified 2642 references of which 912 were duplicates (Figure 1). From the 29 full text papers we accessed to determine eligibility, we found three randomised clinical trials that met our inclusion criteria (Dhabangi 2013; Schulman 2002; Walsh 2004). These trials were published between 2002 and 2013, and were conducted in Uganda (Dhabangi 2013), the United States of America (Schulman 2002), and the United Kingdom (Walsh 2004). The Characteristics of included studies table shows a detailed description of the included trials.

Figure 1. Study flow diagram.



We also identified four ongoing studies (Characteristics of ongoing studies).
Ten study reports from an updated search in June 2015 have been added to Studies awaiting classification.

Included studies

Clinical characteristics

One trial was conducted in adults (Walsh 2004), and one in children (Dhabangi 2013). One trial did not report the age of the participants (Schulman 2002). Two trials reported the gender of the participants (Dhabangi 2013; Walsh 2004). Trials involved people with malaria (Dhabangi 2013), critically ill people with anaemia (Walsh 2004), and people with a traumatic injury (Schulman 2002).

Intervention characteristics

- Packed red cell blood storage definition

1. Long-stored ('older') blood cell use: trials met the criteria of long-stored ('older') blood cells if they were stored for ≥ 21 days (Dhabangi 2013; Schulman 2002; Walsh 2004).
2. Short-stored (fresh) blood cell use:
trials were conducted using different definitions for short-stored (fresh) blood cells: 1 to 10 days (Dhabangi 2013), ≤ 5 days (Walsh 2004) and ≤ 11 days (Schulman 2002).

- Intervention and comparator groups

The intervention and comparator groups differed across the trials. Dhabangi 2013 compared a short storage arm (1-10 days) versus a long storage arm (21-35 days). No information was supplied as to whether the transfused blood was leukodepleted. Schulman 2002 compared leukodepleted packed red blood cells stored for ≥ 21 days since collection, with leukodepleted packed blood cells stored for ≤11 days; participants were transfused within 24 hours of hospitalisation. Walsh 2004 compared 2 units of leukodepleted packed red blood cells stored for ≥ 21 days since collection, with 2 units of leukodepleted packed red blood cells stored for ≤ 5 days.

Outcome characteristics

Data were available for two of our defined outcomes: death from any cause (Dhabangi 2013; Schulman 2002) and incidence of metabolic acidosis (Walsh 2004).

Methodology characteristics

All the trials had a parallel-study design and compared two groups. Each was conducted in a single centre. These trials randomised 127 participants, of which there were outcome data for 113 participants. The duration of follow-up in one trial was 24 hours (Dhabangi 2013). Another trial followed participants for 12 months (Walsh 2004). One trial did not report the follow-up period (Schulman 2002). All trials were conducted without a priori sample size estimation (Dhabangi 2013; Schulman 2002; Walsh 2004) and used participants as both the units of randomisation and analysis (Dhabangi 2013; Schulman 2002; Walsh 2004). All three trials reported inclusion criteria (Dhabangi 2013; Schulman 2002; Walsh 2004). Two trials reported exclusion criteria (Dhabangi 2013; Walsh 2004).

Excluded studies

We excluded 25 studies: eleven trials for having overlapping 'fresh' and 'older' storage criteria, two trials for comparing packed red blood cells versus whole blood, two trials where no information was provided on the duration of storage, one retrospective study, one case series, one case cross-over study and seven observational studies. See Characteristics of excluded studies.

Ongoing trials

We found four ongoing trials (ACTRN12612000453886; ISRCTN08118744; NCT00458783; NTR2662). The Characteristics of ongoing studies table shows full details.

Risk of bias in included studies

The risk of bias in the included trials is summarised in Figure 2 and Figure 3, and detailed in the Characteristics of included studies table.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. Three studies are included in this review.

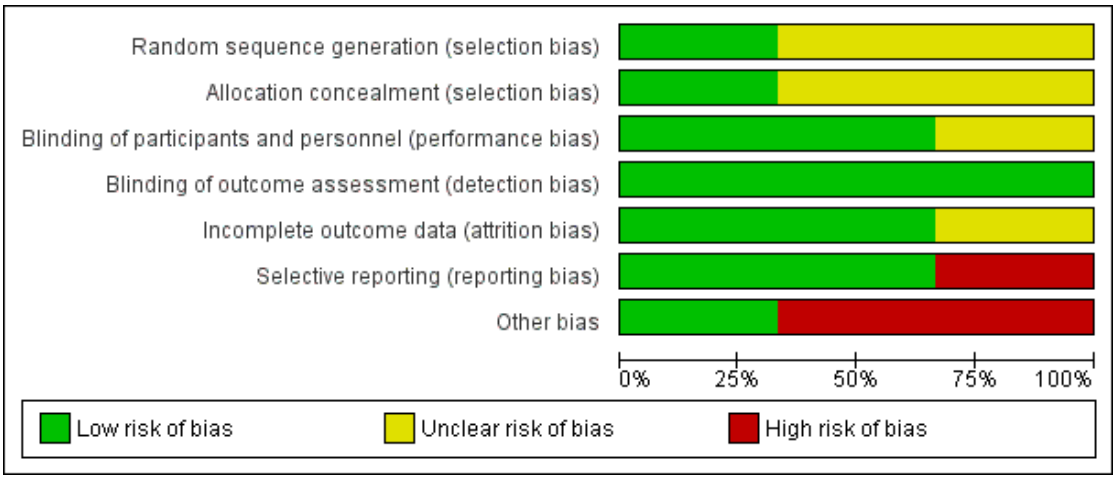
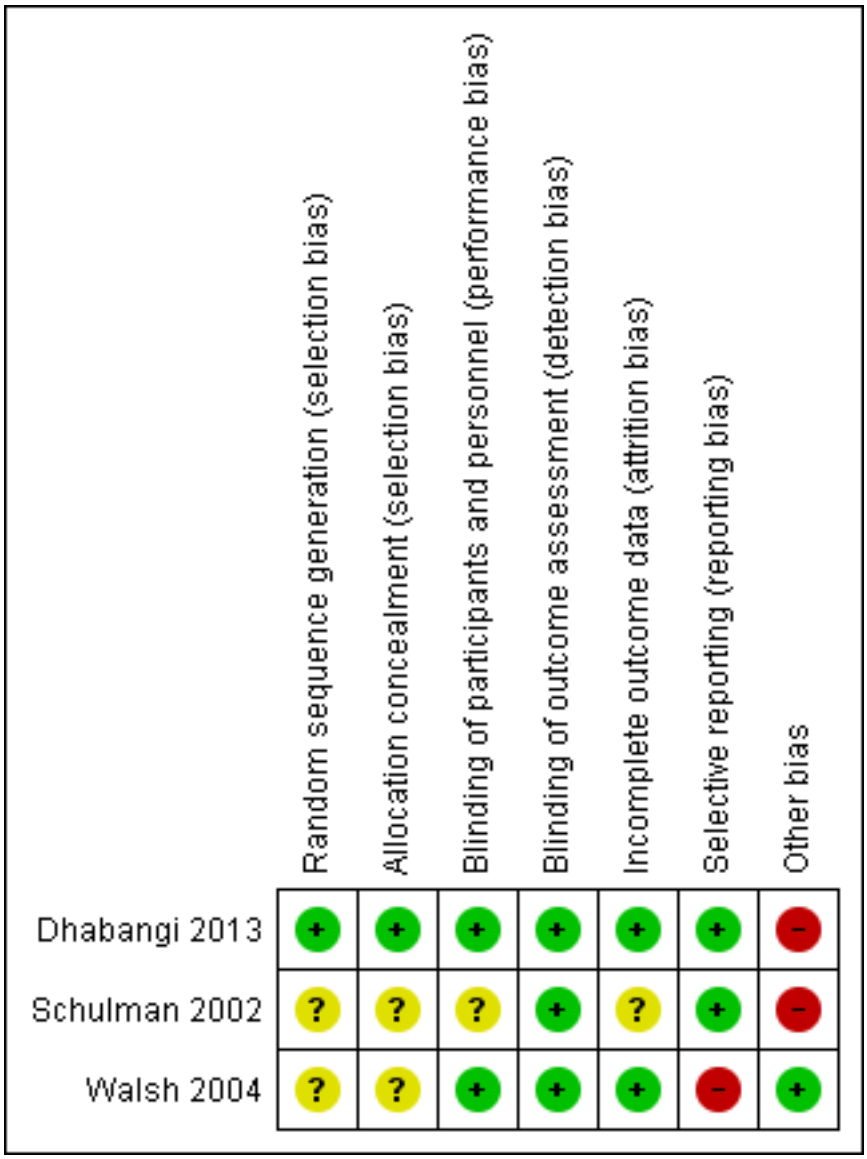


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Generation of the randomisation sequence

One trial was rated as low risk of bias (Dhabangi 2013). The risk of bias arising from the method of generation of the randomisation sequence was rated as unclear risk in two trials (Schulman 2002; Walsh 2004).

Allocation concealment

One trial was rated as low risk of bias (Dhabangi 2013). The risk of bias arising from the method of allocation concealment was unclear in two trials (Schulman 2002; Walsh 2004).

Blinding

We judged all trials to be of low risk of bias in relation to the method of blinded outcome assessment (Dhabangi 2013; Schulman 2002; Walsh 2004).

We judged the risk of bias arising from blinding of the participants and personnel as low in two trials (Dhabangi 2013; Walsh 2004). The risk of bias from blinding was unclear for one trial as insufficient information was provided on which to make a judgement (Schulman 2002).

Incomplete outcome data

The risk of bias arising from incomplete outcome data was low in two trials (Dhabangi 2013; Walsh 2004). This domain was rated as unclear in one trial (Walsh 2004).

Selective reporting

Risk of reporting bias was rated as low as in two trials (Dhabangi 2013; Schulman 2002). This domain was rated as high in one trial, because all the outcomes reported were physiological measurements (Walsh 2004).

Other potential sources of bias

One trial was rated as low risk in this domain (Walsh 2004). One trial had bias in the presentation of data and was rated as high risk (Schulman 2002).

Effects of interventions

See: **Summary of findings for the main comparison** Long-stored ('older') PRBC ($\geq$ 21 days of storage) compared with short-stored (fresh) PRBC (< 21 days of storage) for patients requiring blood transfusion

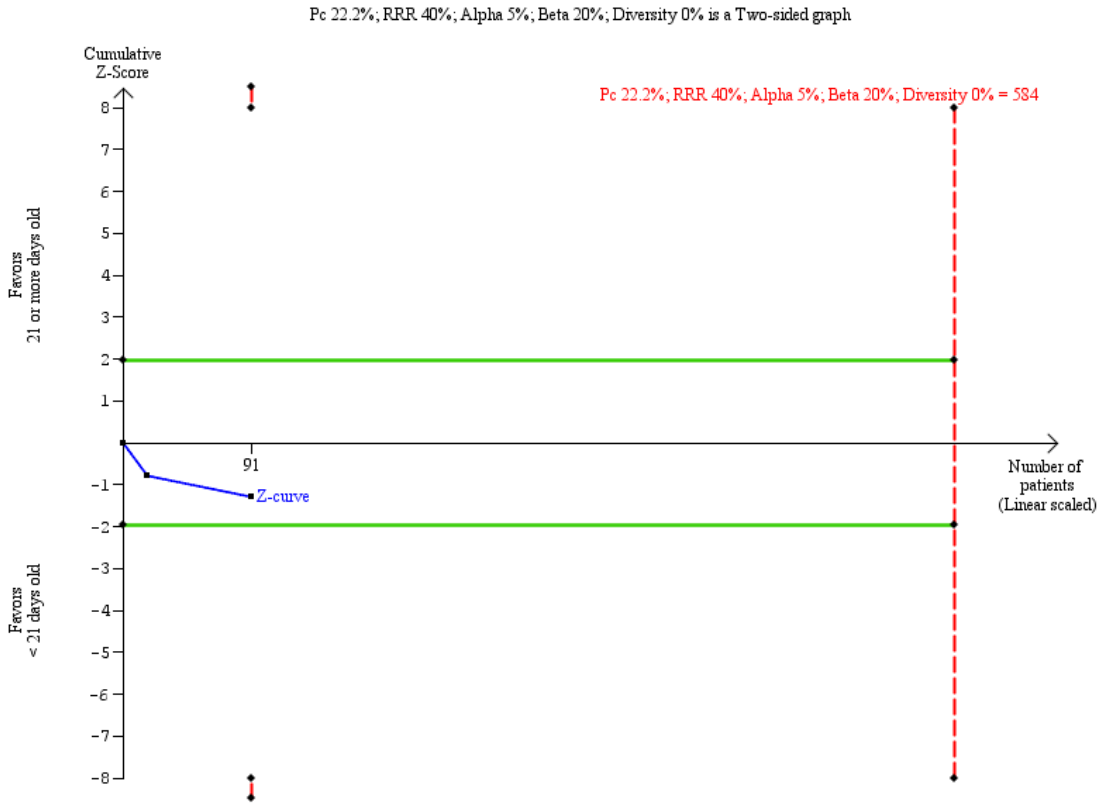
The included trials did not assess the following pre-defined outcomes in this Cochrane Review: multiple organ failure post injury, transfusion-related acute lung injury, postoperative infections, hyperkalaemia, coagulopathy and post-injury coagulopathy.

Primary outcomes

Death from any cause

Meta-analysis of two trials showed no difference in the risk of death among participants receiving packed red blood cells with longer or shorter storage duration (5/45 (11.11%) versus 2/46 (4.34%); (RR 2.36; 95% CI 0.65 to 8.52; I^2: 0%, very low quality of evidence) (Dhabangi 2013; Schulman 2002). See Analysis 1.1. Trial sequential analysis shows that, based on two trials, we have convincing evidence that packed red blood cells with < 21 days of storage are not able to induce a 20% RR reduction of death from any cause compared with red blood cells with $\geq$ 21 days of storage (Figure 4).

Figure 4. Trial sequential analysis on death from any cause in two trials of < 21 day old versus ≥ 21 day old packed red blood cells. Trial sequential analysis of two trials of < 21 day old versus ≥ 21 day old packed red blood cells on death from any cause based on the diversity-adjusted required information size (DARIS) of 584 patients. This DARIS was calculated based upon a proportion of patients with death from any cause of 22.2% in the control group; a RRR of 40% in the experimental intervention group; an alpha (α) of 5%; and a beta (β) of 20%. The cumulative Z-curve (blue line) did not cross the conventional alpha of 5% (green line) after two trials. It implies that there is a random error. The cumulative Z-curve did not reach the futility area, which is not even drawn by the program. Presently, only 2.91% (17/584) of the DARIS has been obtained. Had we calculated the DARIS based on a more realistic RRR such as 20% or less, the obtained evidence would represent a much smaller part of the DARIS.



Secondary outcomes

Metabolic acidosis

One trial (29 participants) reported no important changes in pH and HCO_3^- from the baseline period (2.5 hrs; mean of five measurements) to the post-transfusion period (5 hrs; mean of five measurements). There was no difference in pH values comparing packed red blood cells with ≤ 5 days of storage (median 0.02 [interquartile range (IR) -0.01 to 0.05]) with packed red blood cells with ≥ 21 days of storage (median -0.02 [IR -0.06 to 0.01]). There was no difference in HCO_3^- ([actual], mmol/L) values comparing packed red blood cells with ≤ 5 days storage (median -0.85 [IR -1.44 to -0.53]) with ≥ 21 days of storage (median -0.29 [IR -0.90 to 0.07]) (Walsh 2004).

DISCUSSION

Summary of main results

We identified three randomised clinical trials involving 120 participants. These trials were conducted in Uganda, the USA, and the UK. One trial was conducted in children (Dhabangi 2013), one in adults (Walsh 2004), and the other trial did not report the age of the participants (Schulman 2002). Over 60% of the participants were male in the one trial reporting this variable (Walsh 2004). Trials involved people with malaria, critically ill people with anaemia, and people with a traumatic injury. One trial had low risk of bias (Dhabangi 2013), the other two trials had a high risk of bias (Schulman 2002; Walsh 2004). All trials were underpowered. Furthermore, they were conducted in a single centre.

Meta-analysis of two trials on the outcome death from any cause found no difference between 'fresher' red blood cells (< 21 days) compared with 'older' packed red blood cells (≥ 21 days) (Dhabangi 2013; Schulman 2002). One trial reporting metabolic acidosis showed no difference between 'fresh' packed red blood cells (< 21 days) compared with 'older' packed red blood cells (≥ 21 days of storage) (Schulman 2002).

None of the trials reported data on two of the review's pre-planned primary outcomes: transfusion-related acute lung injury and post-operative infections. There was no information about safety and so adverse events may be underestimated. Furthermore, included trials did not address coagulopathy, post-injury coagulopathy, multiple organ failure post-injury, hyperkalaemia, or quality of life.

Overall completeness and applicability of evidence

This Cochrane Review provides inconclusive evidence on the clinical effectiveness and safety of prolonged storage of red blood cells compared with fresh red blood cells for blood transfusion. This conclusion is based on three small single centre trials with inadequate information provided by trial reports on patient-important outcomes. These methodological issues have a negative impact on effectiveness trials (Hopewell 2010). We feel those issues are particularly relevant to consider as further work on the topic is planned. In this regard, it has been suggested that trials should adopt an agreed set of core outcomes for each medical condition to enable generation of information that is relevant and trustworthy for patients, and to enable decisions that improve patient-important outcomes (Basch 2012; Clarke 2007; Selby 2012). The meta-analysis assessing the effect of interventions on death from any cause included participants with different characteristics, i.e. children with malaria and people with a traumatic injury (Dhabangi 2013; Schulman 2002). In the future when more studies are included in this review, the review will include data from people with additional different characteristics which will make the results more relevant across all populations.

Quality of the evidence

GRADE assessments were conducted on the pre-specified outcomes. None of the trials were graded as providing strong evidence because of small sample size, lack of measurement of important clinical outcomes in the included trials (reporting bias), high risk of selection bias, or bias in the presentation of data, sample bias or design bias. Our assessment of the risk of bias of the included studies has been described previously and is summarised in the Risk of bias in included studies table and Figure 2 and Figure 3. See Summary of findings for the main comparison for the complete rationale for the ratings.

Potential biases in the review process

Systematic reviews are predisposed to have a 'significance-chasing bias' (Ioannidis 2010). This includes publication bias, selective outcome reporting bias, selective analysis reporting bias, and fabrication bias (Ioannidis 2010). We tried to reduce the risk of such biases affecting the results of this review by completing a thorough search for studies. Selective outcome reporting bias operates through suppression of information on specific outcomes and has similarities to publication bias, in that 'negative' results remain unpublished (Ioannidis 2010). This review found that one out of the three included trials has high risk of selective outcome reporting (Walsh 2004), because it only reported physiological measurements.

Agreements and disagreements with other studies or reviews

Despite differences in the methodology, this review has the same findings as Frenzel 2009 who pointed out the uncertainty about the true clinical impact of the role of prolonged storage of red blood cells on the microcirculation and tissue oxygenation in critically ill patients. In addition, Yap 2008 suggested that age of transfused red cells is not associated with early mortality and morbidity after cardiac surgery. Furthermore, this systematic review has addressed the queries on need to assess the methodological quality of trials and the duration of storage of red blood cells for transfusion in any clinical setting. The debate on whether transfusion of 'older' blood is as beneficial as transfusion of 'fresher' blood, as described by Glynn 2010, continues.

AUTHORS' CONCLUSIONS

Implications for practice

Recognising the limitations of the review, relating to the size and nature of the included trials, this Cochrane Review provides no

evidence to support or reject the use packed red blood cells stored for more or less than 21 days. These results are based on three small single centre trials at high risk of bias. There is insufficient evidence to determine the effects of 'fresher' or 'older' packed red blood cells for blood transfusion. Therefore, we urge readers to interpret the trial results with caution. The results from four large ongoing trials will help to inform future versions of this review.

Implications for research

Currently, four larger trials are being conducted in different clinical settings to assess the impact of prolonged storage of packed red blood cells for blood transfusion (ACTRN12612000453886; ISRCTN08118744; NCT00458783; NTR2662). These trials will contribute substantially to our understanding of the effects of these different approaches to transfusion. Any further studies should be well-designed, high-quality randomised trials which explicitly define 'short' and 'long' storage periods, and measure patient-important outcomes such as mortality from any cause, transfusion-related acute lung injury, postoperative infections, coagulopathy, post-injury coagulopathy, multiple organ failure post-injury and harms outcomes (hyperkalaemia and metabolic acidosis) as recommends the Methodology Committee of the Patient-Centered Outcomes Research Institute (PCORI) (Basch 2012; Cohen 2013). The results of these ongoing trials could change the conclusions of this Cochrane Review.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Dhabangi 2013

Methods	Design: parallel (2 arms) Country: Kampala, Uganda Site: one site (Acute Care Unit, the paediatric emergency unit of Mulago Hospital) Follow up: 24 hours Randomisation unit: patient Unit of analysis: patient
Participants	Population: children aged six months to 59 months Enrolled and randomised: 74 Analysed: 74 1. Age (Age (months), mean (SD)) • Short storage: 27.6 (16.6) • Long storage: 23.1(15.2) 2. Gender (female, n (%)) • Short storage: 22 (59.5%) • Long storage: 14 (37.8%) 3. Haemoglobin (g/dL) • Short storage: 4.0 (0.9) • Long storage: 3.7 (0.8) 4. Quantitative parasite count (median, interquartile range) • Short storage: 19,760 (9,680 and 78,120) • Long storage: 18,440 (3,200 and 57,600) 5. Inclusion criteria: • Positive blood smear for malaria • Severe anaemia (Hb $\leq$ 5 g/dL) • Lactic acidosis (blood lactate $\geq$ 5 mmol/L) • Written informed consent from the parent or guardian 6. Exclusion criteria: • Known or concurrent cardiac disease • Undergoing transfusion with blood products other than packed red cells
Interventions	Short storage packed red blood cells (one to 10 days) Long storage packed red blood cells (21-35 days) All patients received intravenous quinine as routine standard treatment for severe malaria
Outcomes	1. Primary outcome measures: • Lactic acidosis resolution within four hours from the start of the transfusion 2. Secondary outcome measures: • Deaths within 24 hrs. This data was gathered from clinicaltrials.gov web site (http://clinicaltrials.gov/show/NCT01580111)
Notes	1. Trial registration: clinicaltrials.gov NCT01580111 2. Conduction date: December 2010 and August 2011 3. A priori sample size estimation: no

Dhabangi 2013 (*Continued*)

	4. Sponsor: supported in part by scholarship grants from the Belgian Technical Co-operation (BTC) and the Carnegie next generation of academics project 2010 - 2012 5. Competing interests: The authors declare that they have no competing interests This trial is linked with NCT01586923. See http://clinicaltrials.gov/show/NCT01586923 for details

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The trial authors describe a random component in the sequence generation process such as shuffling envelopes Comment: trial author supplied information
Allocation concealment (selection bias)	Low risk	Quote "these were thick paper envelopes and so the only way to see the assignment was to open the envelope" Comment: trial author supplied information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open trial, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open trial, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias)	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Trial reported outcomes (clinical and surrogate)
Other bias	High risk	Sampling bias and design bias

Schulman 2002

Methods	Design: parallel (2 arms) Country: USA (1 site) Follow up: not given Randomisation unit: patient Unit of analysis: patient

Schulman 2002 (*Continued*)

Participants	Population: trauma patients 1. Enrolled: 8000 2. Randomised: 24 3. Analysed: 17 (”were transfused two or more units of type-specific blood“) 4. Lost to follow-up: 7 (causes not described) • Treatment arm: 47% (8/17) • Control arm: 53% (9/17) 5. Age (years ±(SD)): not reported 6. Gender (male %): not reported 7. Inclusion criteria: • If blood bank had at least 15 units of both young and old blood available 8. Exclusion criteria: not given
Interventions	1. Intervention group: • Leucocyte-depleted type-specific ”young“ (< 11 days) blood 2. Control group: • Leucocyte-depleted type-specific ”old“ (> 20 days) blood
Outcomes	Not described as ”primary or secondary“ • Death • Complications (”Data on infectious complications, respiratory failure and outcome were collected“)
Notes	1. A priori sample size estimation: no 2. Sponsor: not reported 3. Conducted between August 2000 and July 2001 at level I trauma center ”Because of availability of blood types found during an inventory of our blood bank, it was predetermined that only patients with A type blood would be studied (approximately 40% of the U.S. population)“ 4. Data were gathered from editor letter 5. Declared conflict of interest: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk' Quote ”Patients were randomized to receive...“
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgment of 'Low risk' or 'High risk'

Schulman 2002 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: According to a recent study (Wood 2008), this might be irrelevant when the outcomes are objective as it is the case in this randomised clinical trial
Incomplete outcome data (attrition bias)	Unclear risk	Quote: "...only 24 patients presenting to the trauma center could be randomised because of blood bank inventory limitations. Of these, 17 patients were transfused two or more units of type-specific blood" Comment: All participants who were randomised and who received the trial specified 2 units of red blood cells were included in the analysis. Although 30% (n=7) of participants are not accounted for in the analysis, it appears that they did not receive the intervention and thus all the outcome data expected to be available at the end of the study are available
Selective reporting (reporting bias)	Low risk	This trial reported death "There were not statistically significant differences in complications between these two small groups." Information on safety: not given
Other bias	High risk	Bias of presentation data, sample bias and design bias (Porta 2008)

Walsh 2004

Methods	Design: parallel (2 arms) Country: Edinburgh, Scotland (1 site) Follow up: 12 months Randomisation unit: patient Unit of analysis: patient
Participants	Population: anemic critically ill patients 1. Enrolled: 50 2. Randomised: 29 3. Loss post-randomisation (no transfusion given): 24.1% (7/29) 4. Analysed: 22 patients in the analysis based upon treatments received: • Experimental: 10 (45.4%) • Control: 12 (54.5%) 5. Age: • Experimental group (receiving red blood cells 5 days of age or less): 55±11.4 yr

	• Control group: 60.5± 12.35 yr 6. Gender (Number of women) • Experimental group: 30% (3/10) • Control group: 41.6% (5/12) 7. Inclusion criteria: • Intensive care physician caring for the patient decided to transfuse two units of red cells to increase the haemoglobin concentration in the absence of clinically obvious bleeding • Transfusion could be deferred 12-18 hrs to enable relatives' assent to be sought where necessary and randomisation to be done • Haemoglobin concentration at the time of screening was ≤ 90 g/L • Patient had not received a red cell transfusion for at least 48 hrs before the baseline measurements were to start 8. Exclusion criteria: • Presence of clinically apparent bleeding • Contraindication to placement of a nasogastric tube • Patient required frequent changes in respiratory or cardiovascular support due to physiologic instability • Patient was not expected to survive > 24 hrs • Previous gastric surgery • Postoperative liver transplant patient • Age ≤ 16 yrs • Pregnancy
Interventions	1. Experimental: two units of leukodepleted red cells collected ≤ 5 days before the planned start of the study transfusion 2. Control: two units collected ≥ 20 days before the planned start of the study transfusion
Outcomes	1. Primary: The intragastric-arterial difference in PCO_2 (Pg-$PaCO_2$ gap) during and after the red cell transfusion using air tonometry 2. Secondary: Physiologic variables: pHi, arterial lactate, concentration, $PaCO_2$, arterial pH, and arterial base excess. Changes in arterial haemoglobin concentration during the study period were also compared
Notes	1. A priori sample size estimation: "We chose to randomize 22 patients to ensure ten patients per group. This number was chosen pragmatically based on a) the supposition that the effect observed by Marik and Sibbald would be reproduced (page 365) 2. Dates the study took place: November 1999 and December 2000 3. Sponsor: Mason Medical Research Foundation, the Effective Use of Blood Group of the Scottish National Blood Transfusion Service and from the Royal Infirmary of Edinburgh Intensive Care Unit Research Fund 4. Declared conflicts of interest: no

Risk of bias

Bias	Authors' judgement	Support for judgement

Walsh 2004 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote "Random-length block randomization ..." (page 365) Insufficient information to permit judgment of 'Low risk' or 'High risk'
Allocation concealment (selection bias)	Unclear risk	Quote "Nonresealable envelopes..." (page 365) Insufficient information to permit judgment of 'Low risk' or 'High risk'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote " To ensure that all individuals in the ICU were blinded to the age of the transfused units, special blood pack labels and forms were printed for the study. These obscured the collection and expiry dates, but stated a time within which the blood must be transfused, which allowed full checking before administration" (page 365)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: According to a recent study (Wood 2008), this might be irrelevant when the outcomes are objective as it is the case in this randomised clinical trial
Incomplete outcome data (attrition bias)	Low risk	Comment: All randomised participants who received a red blood cell transfusion were included in the outcome analyses 24% (n=7) of participants were randomised but did not receive a red blood cell transfusion for the following reasons: Older blood subsequently unavailable: 2 participants Assent withdrawn: 1 participant Technical problem: 2 participants Clinical deterioration: 2 participants. (Figure 2, page 366). These participants were not included in the outcome assessment for this trial
Selective reporting (reporting bias)	High risk	This trial only assessed physiologic variables
Other bias	Low risk	-

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ARIPI 2012	There is an overlap between 'fresh' and 'older' storage Comment: We excluded randomised clinical trials where patients received a combination of short- and long-stored blood products
Aubron 2012	The authors did not define 'prolonged' storage in this randomised clinical trial
Bennett-Guerrero 2009	There is an overlap between 'fresh' and 'older' storage Comment: We excluded randomised clinical trials where patients received a combination of short- and long-stored blood products
Cartotto 2014	Observational study
Cunha 2004	There is an overlap between 'fresh' and 'older' storage Comment: We excluded randomised clinical trials where patients received a combination of short- and long-stored blood products
Dunn 2012	Observational study
Eshleman 1994	There is an overlap between 'fresh' and 'older' storage Comment: We excluded randomised clinical trials where patients received a combination of short- and long-stored blood products
Fernandes 2005	This trial has an overlap between both storage periods "26 newborns were randomly assigned to Group 1 and were transfused with CPDA-1 RBC stored for up to 28 days; 26 newborns were assigned to Group 2 and received CPDA-1 RBC stored for at most 3 days." There is an overlap between 'fresh' and 'older' storage Comment: We excluded randomised clinical trials where patients received a combination of short- and long-stored blood products
Gomez-Lesmes 2014	Observational study
Hebert 2005	There is an overlap between 'fresh' and 'older' storage Comment: We excluded randomised clinical trials where patients received a combination of short- and long-stored blood products
Heddle 2012	Authors did not define 'fresh' or 'older' threshold in this study
Juffermans 2012	Observational study
Kadar 2013	Observational study
Kaukonen 2013	Observational study
Kekre 2013	Observational study

(*Continued*)

Kor 2012	Quote "The intervention (fresh versus standard issue storage duration) was only for the first red blood cell unit administered after randomisation. All subsequent red blood cell transfusions were standard issue." Comment: We excluded RCTs where patients received a combination of short- and long-stored blood products
Liu 1994	There is an overlap between 'fresh' and 'older' storage Comment: We excluded randomised clinical trials where patients received a combination of short- and long-stored blood products
Marcus 1985	This randomised clinical trial compared packed red blood cells versus whole blood
Min 2014	Retrospective study
Rogers 2014	Within-person case crossover study
Strauss 1996	There is an overlap between 'fresh' and 'older' storage Comment: We excluded randomised clinical trials where patients received a combination of short- and long-stored blood products
Strauss 1999	There is an overlap between 'fresh' and 'older' storage Comment: We excluded randomised clinical trials where patients received a combination of short- and long-stored blood products
Wallis 2005	Quote "Patients in arm A received blood that had been stored for greater then 24 to 35 days for the first two transfusions ('old blood'), and blood that had been stored for less than 10 days for the second two transfusions ('new blood'). Patients in arm B received new blood for the first two transfusions and old blood for the second two transfusions." Personal communication with Dr Wallis Comment: We excluded RCTs where patients received a combination of short- and long-stored blood products
Wasser 1989	Randomised clinical trial conducted using whole blood
Weinberg 2013	Case series

Characteristics of studies awaiting assessment *[ordered by study ID]*

Damiani 2015

Methods	RCT, secondary analysis
Participants	20 adult septic patients
Interventions	'Fresh' or 'old' RBC transfusions (<10 or >15 days storage respectively)
Outcomes	

Damiani 2015 (*Continued*)

Notes	

Klein 2014

Methods	
Participants	
Interventions	
Outcomes	
Notes	Paper to be acquired

Lacroix 2011

Methods	Study design
Participants	
Interventions	
Outcomes	
Notes	Protocol for ABLE study

Lacroix 2015

Methods	RCT
Participants	Anemic inpatients
Interventions	RBC stored <14 days or RBC stored >21 days
Outcomes	
Notes	ABLE study

Neuman 2013

Methods	
Participants	
Interventions	
Outcomes	

Notes	Paper to be acquired

Neuman 2015

Methods	RCT
Participants	Anemic inpatients
Interventions	Fresh (<14 days) or older (>21 days) RBC units
Outcomes	
Notes	

Redlin 2014

Methods	
Participants	Paediatric cardiac surgery
Interventions	26 patients received RBCs stored for ≤3 days 126 patients received RBCs stored for 4-14 days
Outcomes	
Notes	

Steiner 2015

Methods	RCT
Participants	Cardiac surgery
Interventions	Leukocyte-reduced red cells stored ≤10 days v ≥21 days
Outcomes	Multiple Organ Dysfunction Score
Notes	

Thurer 2013

Methods	
Participants	
Interventions	

Thurer 2013 (*Continued*)

Outcomes	
Notes	Paper to be acquired

Von Heymann 2013

Methods	
Participants	
Interventions	
Outcomes	
Notes	Paper to be acquired

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12612000453886

Trial name or title	Standard issue transfusion versus fresher red blood cell use in intensive care - a randomised controlled trial
Methods	• Randomised controlled trial The treatment allocation will be determined using variable block randomisation in a 1:1 ratio, stratified by centre • Blinded (masking used) 1. The people receiving the treatment/s 2. The people administering the treatment/s 3. The people assessing the outcomes 4. The people analysing the results/data
Participants	Age: ≥ 18 years Sex: both • Inclusion criteria: Patients hospitalised in intensive care unit with an anticipated intensive care unit stay of at least 24 hours, in whom the decision has been made by medical staff to transfuse at least one red blood cell (RBC) unit • Exclusion criteria: 1. Age younger than 18 2. A previous RBC transfusion during the current hospital admission (including transfusion in another hospital for transferred patients) 3. Diagnosis of transplantation or hematologic diseases 4. Pregnancy 5. Cardiac surgery during the present hospital admission 6. Expected to die imminently (< 24hrs) 7. The treating physician believes it is not in the best interest of the patient to be randomised in this trial 8. Known objection to the administration of human blood products

ACTRN12612000453886 (*Continued*)

Interventions	Experimental: freshest available group-specific compatible RBC unit in the transfusion service. Indication, timing and number of RBC units will be determined as per standard practice by the clinician for each individual situation Control: no intervention; standard of care. These patients will receive standard practice, which is the oldest available group-specific compatible RBC unit in the transfusion service
Outcomes	Primary: mortality of patients admitted to the intensive care unit measured at 28 and 90 days post-intervention Secondary: persistent organ dysfunction combined with death at day 28 defined as number of days requiring mechanical ventilation, renal replacement therapy and catecholamines at day 28
Starting date	Anticipated or actual date of first participant enrolment: 1/10/2012
Contact information	Bridget Ady. School of Public Health & Preventive Medicine, Monash University. L6, The Alfred Centre, 'B' Lobby (via Centre Lane) 99 Commercial Road, Melbourne VIC 3004 E-mail: bridget.ady@monash.edu
Notes	Phase: 3 Target sample size: 5000 Recruitment status: not yet recruiting (10 September 2012) Funding source: Government funding body e.g. Australian Research Council. National Health Medical Research Council Sponsor: Monash University. Department of Epidemiology & Preventive Medicine. School of Public Health & Preventive Medicine. Monash University, The Alfred Centre 99 Commercial Road, Melbourne VIC 3004. Australia

ISRCTN08118744

Trial name or title	Public title: Informing fresh versus standard issue red cell management (INFORM) Scientific title: INforming Fresh versus Old Red cell Management (INFORM): a large simple phase III randomized controlled trial Countries: Australia, Canada, United States of America
Methods	Multi-centre international randomised controlled trial
Participants	• Inclusion criteria: All adult patients (age >/= 18) will be included if: 1. Hospitalised at a participating centre (in-patient) 2. Undergoing a red cell transfusion • Exclusion criteria: 1. Specific requirement for fresh blood (e.g., sickle cell disease, transfusion-dependent thalassaemia, fresh cells ordered by care provider) 2. Pre-planned directed or autologous donation 3. Request for un-crossmatched blood 4. Anticipated massive transfusion as communicated from clinical area
Interventions	Patients requiring red blood cell transfusion will be randomised to one of the following conditions: 1. Freshest available red blood cells (experiment arm) 2. Standard-issue (oldest product compatible in stock) red blood cells available (control arm)

ISRCTN08118744 (*Continued*)

	Both arms (experiment and control) are within standard care
Outcomes	Primary: in-hospital mortality Secondary: time to event (death)
Starting date	Date of first enrolment: Jan 16 2012
Contact information	Source(s) of monetary support: Canadian Institutes of Health Research [CIHR] (Canada) Primary sponsor: McMaster University (Canada) Rebecca Barty. Clinical Research Coordinator McMaster Transfusion Research Program McMaster University Faculty of Health Sciences Department of Medicine HSC-3H50 1280 Main Street West L8S 4K1, Hamilton, Canada. bartyr@macmaster.ca
Notes	Target sample size: 24,400 Recruitment status: ongoing/recruiting

NCT00458783

Trial name or title	Official title: Red cell storage duration and outcomes in cardiac surgery Condition: blood transfusion, cardiac surgery
Methods	• Study type: intervention • Study design: RCT 1. Allocation: randomised 2. Endpoint classification: efficacy study 3. Intervention model: parallel assignment 4. Masking: double blind (participant, outcomes assessor)
Participants	Estimated enrolment: 2800 Ages eligible for study: 18 years and older Genders eligible for study: both Accepts healthy volunteers: No • Inclusion criteria: All primary and reoperative adult cardiac surgical patients undergoing cardiopulmonary bypass for coronary artery bypass grafting, coronary artery bypass grafting with a valve procedure, and isolated valve procedures • Exclusion criteria: 1. Age less than 18 years 2. Descending thoracic aortic aneurysm repairs 3. Left or right ventricular assistive devices 4. Unable to receive blood for religious reasons
Interventions	Group A: red blood cell transfusion with blood cell storage duration less than 14 days Group B: red blood cell transfusion with blood cell storage duration more than 20 days
Outcomes	Postoperative morbidity outcomes

NCT00458783 (*Continued*)

Starting date	Study completion date: April 2007 Primary outcome data collection date: February 2014 Last updated: May 8, 2012
Contact information	Outcomes Research Consortium Principal Investigator: Collen G. Koch, MD, MS. The Cleveland Clinic
Notes	This study is currently recruiting participants Sponsor: Outcomes Research Consortium

NTR2662

Trial name or title	Public title: Age of Blood evaluation Scientific title: Age of Blood evaluation, resuscitation in the critically ill (ABLE-NL)
Methods	Randomised: yes Masking: double Control: active Group: parallel Type: 2 or more arms, randomised
Participants	• Inclusion criteria: 1. Have had a request for a first red cell unit transfusion in the intensive care unit (or in the emergency department after admission to the intensive care unit was requested by an intensivist), and 2. Have an anticipated length of invasive and/or non-invasive mechanical ventilation of at least 24 hours, once enrolled, as estimated by the attending physician • Exclusion criteria: 1. Less than 18 years of age 2. For whom there is verbal or written report of a red cell transfusion during the current hospitalisation (including time in emergency room, or during transport in an ambulance, or time in another hospital prior to the transfer, whatever the length of the first hospitalisation is) 3. Who have an obvious terminal illness documented in the medical record with a life expectancy less than 3 months 4. Where a decision to withdraw or withhold some care has been made (patients who have a DNR but no other treatment restrictions can be included!) 5. Is obviously brain dead 6. Who have a known objection to blood transfusion 7. Who had a transfusion with autologous donation of blood 8. Who is already enrolled in a competing trial 9. Whose attending intensivist refused patient's participation in the ABLE study Blood bank personnel will also exclude: 1. Patients who were previously enrolled in the ABLE study 2. When there are no available red cells with storage time of 7 days or less compatible with this patient blood group in the blood bank and that cannot be transported from the blood supplier 3. Patients who require more than 1 unit of uncross-matched cells, who pose difficulties in securing blood products (rare blood groups or difficult to crossmatch)

NTR2662 (*Continued*)

Interventions	1. Red cells according to standard procedure (storage time 2-35 days) 2. "Fresher" red cells (storage time: 2-8 days)
Outcomes	• Primary: the primary analysis will be on nosocomial infections, especially pneumonia. Pneumonia is the only clinical endpoint that has been reported more than once to remain statistically significantly correlated with storage time, even after adequate correction for total number of RBC transfusions. Increases in pneumonia of up to 6% for each additional day of storage have been reported • Secondary: as compared to standard issue red cells, we will ascertain whether red cells stored 7 days or less: 1. Decrease in-hospital, intensive care unit, 28-day, 90-day and 6-month mortality; 2. Decrease the severity of multiple organ dysfunction syndrome, as measured by the number of organ dysfunction and multiple organ dysfunction syndrome score 3. Decrease serious nosocomial infections 4. Reduce the length of intensive care unit and hospital stays 5. The occurrence of allo immunisation after transfusion of red cells 6. Special attention will also be paid to red cell transfusions and transfusion reactions
Starting date	Date of registration: 22/12/2010 Date of first enrolment: 1/3/2011
Contact information	E.K. Hogervorst Email: e.hogervorst@sanquin.nl Plesmanlaan 1a, Sanquin Leiden, afdeling O&O 2333 BZ Leiden, the Netherlands
Notes	Country: The Netherlands Primary sponsor: Sanquin Blood Bank South West Region Target sample size: 2000 Source(s) of monetary support: Sanquin Blood Supply, ABLE study group - Canada

DATA AND ANALYSES

Comparison 1. <21 days old versus ≥21 days old packed red blood cells

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death from any cause	2	91	Risk Ratio (M-H, Random, 95% CI)	2.36 [0.65, 8.52]

Analysis 1.1. Comparison 1 <21 days old versus ≥21 days old packed red blood cells, Outcome 1 Death from any cause.

Review: Prolonged storage of packed red blood cells for blood transfusion

Comparison: 1 <21 days old versus ≥21 days old packed red blood cells

Outcome: 1 Death from any cause

Study or subgroup	< 21 days old n/N	≥21 days old n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Dhabangi 2013	1/37	0/37		16.4 %	3.00 [0.13, 71.34]
Schulman 2002	4/8	2/9		83.6 %	2.25 [0.55, 9.17]
Total (95% CI)	**45**	**46**		**100.0 %**	**2.36 [0.65, 8.52]**

Total events: 5 (< 21 days old), 2 (≥21 days old)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.03$, df = 1 (P = 0.87); $I^2 = 0.0\%$

Test for overall effect: Z = 1.31 (P = 0.19)

Test for subgroup differences: Not applicable

APPENDICES

Appendix 1. Non-infectious serious hazards of transfusion

Immune mediated (Hendrickson 2009)	**Non-immune mediated** (Hendrickson 2009)
• Haemolytic transfusion reactions • Febrile non-haemolytic transfusion reactions • Allergic/urticarial/anaphylactic transfusion reactions • Transfusion-related acute lung injury • Post transfusion purpura • Transfusion-associated graft versus host disease • Microchimerism • Transfusion-related immunomodulation • Alloimmunisation	• Septic transfusion reactions • Non-immune haemolysis • Mistransfusion • Transfusion-associated circulatory overload • Metabolic derangements • Coagulopathic complications from massive transfusion • Complications from red cell storage lesions • Over/undertransfusion • Iron overload

Appendix 2. The red blood cell storage solutions

Type (Hess 2006)	**Typical recovery**	**Haemolysis**
• **Three-week storage** Acid citrate dextrose Citrate phosphate dextrose	75% 79%	0.1% 0.1%
• **Five-week storage** Citrate phosphate dextrose plus adenine Citrate phosphate dextrose plus adenine/ saline adenine glucose	72% 83%	0.5% 0.6%
• **Six-week storage** Citrate phosphate dextrose with adenine and extra dextrose Citrate phosphate dextrose/saline adenine glucose plus mannitol High-dextrose citrate phosphate dextrose/ additive solution-3	80% 78% to 84% 78% to 84%	- 0·4% 1.0%
• **Seven-week storage** Citrate phosphate dextrose/phosphate, adenine, glucose, guanosine, saline and mannitol Half-volume citrate phosphate dextrose/re-search additive solution-2	74% 78%	0.5% 0.5%

(*Continued*)

• **Eight-week storage** Citrate phosphate dextrose/EAS-81	85%	0.4%

Appendix 3. Glossary of medical terms

Terms	Definition	Source
Acid citrate dextrose	Used as blood preservative; a mixture of dextrose, citric acid and trisodium citrate	http://www.ncbi.nlm.nih.gov/mesh
Adenosine 5′-triphosphate	An adenine nucleotide containing three phosphate groups esterified to the sugar moiety	http://www.ncbi.nlm.nih.gov/mesh
Blood coagulation	(Blood clotting) the process whereby blood is converted from a liquid to a solid state. The process may be initiated by contact of blood with a foreign surface (intrinsic system) or with damaged tissue (extrinsic system)	Concise Medical Dictionary 2011
Blood coagulation disorders	Haemorrhagic and thrombotic disorders that occur as a consequence of abnormalities in blood coagulation due to a variety of factors such as coagulation protein disorders; blood platelet disorders; blood protein disorders or nutritional conditions	http://www.ncbi.nlm.nih.gov/mesh
Cardiac arrhythmia	Any deviation from the normal rhythm (sinus rhythm) of the heart	Concise Medical Dictionary 2011
Citrate	The salts of citric acid (citrates) can be used as anticoagulants due to their calcium chelating ability	http://www.ncbi.nlm.nih.gov/mesh
Citrate phosphate dextrose	Anticoagulant used in blood preservation	http://www.ncbi.nlm.nih.gov/mesh
Coagulation factors	(Clotting factors) a group of substances present in blood plasma that, under certain circumstances, undergo a series of chemical reactions leading to the conversion of blood from a liquid to a solid state	Concise Medical Dictionary 2011
2,3-Diphosphoglycerate	A highly anionic organic phosphate which is present in human red blood cells at about the same molar ratio as haemoglobin. It binds to deoxyhaemoglobin but not the oxygenated	http://www.ncbi.nlm.nih.gov/mesh

(*Continued*)

	form, therefore diminishing the oxygen affinity of haemoglobin. This is essential in enabling haemoglobin to unload oxygen in tissue capillaries	
Glucose	A primary source of energy for living organisms. It is naturally occurring and is found in fruits and other parts of plants in its free state. It is used therapeutically in fluid and nutrient replacement	http://www.ncbi.nlm.nih.gov/mesh
Haemolysis	The destruction of erythrocytes by many different causal agents such as antibodies, bacteria, chemicals, temperature, and changes in tonicity	http://www.ncbi.nlm.nih.gov/mesh
Hyperkalaemia	The presence in the blood of an abnormally high concentration of potassium	Concise Medical Dictionary 2011
Hypoxaemia	Reduction of the oxygen concentration in the arterial blood	Concise Medical Dictionary 2011
Immnusuppression	Deliberate prevention or diminution of the host's immune response. It may be nonspecific as in the administration of immunosuppressive agents (drugs or radiation) or by lymphocyte depletion or may be specific as in desensitisation or the simultaneous administration of antigen and immunosuppressive drugs	http://www.ncbi.nlm.nih.gov/mesh
Metabolic acidosis	Condition in which the acidity of body fluids and tissues is abnormally high. This arises because of a failure of the mechanisms responsible for maintaining a balance between acids and alkalis in the blood	Concise Medical Dictionary 2011
Multiple organ failure	A progressive condition usually characterised by combined failure of several organs such as the lungs, liver, kidney, along with some clotting mechanisms, usually post-injury or postoperative	http://www.ncbi.nlm.nih.gov/mesh
Platelet activating factor	A phospholipid derivative formed by platelets; basophils; neutrophils; monocytes; and macrophages. It is a potent platelet aggregating agent and inducer of systemic anaphylactic symptoms, including hypotension; thrombocytopenia; neutropenia; and bronchoconstriction	http://www.ncbi.nlm.nih.gov/mesh

(*Continued*)

Post-injury coagulopathy	(1) Prothrombin time (PT) more than 18 seconds; (2) activated partial thromboplastin time (aPTT) more than 60 seconds; (3) PT/aPTT > 1.5 (1.6) control values; (4) international normalised ratio (INR) > 1.2 (PT); (5) INR > 1.5 (PT); (6) quick value of more than 70% (PT)	Stahel 2009
Red blood cell or erythrocyte	A blood cell containing the red pigment haemoglobin, the principal function of which is the transport of oxygen. A blood cell containing the red pigment haemoglobin, the principal function of which is the transport of oxygen	Concise Medical Dictionary 2011
Recovery	Fraction of the injected cells that circulate after infusion and their survival is the length of time that either the average cell or the longest surviving cell circulate. This term is used in Transfusion Medicine	Zimrin 2009
Rheology	The study of the deformation and flow of matter, usually liquids or fluids, and of the plastic flow of solids. The concept covers consistency, dilatancy, liquefaction, resistance to flow, shearing, thixotrophy, and viscosity	http://www.ncbi.nlm.nih.gov/mesh
Transfusion-related acute lung injury	Acute respiratory distress, moderate to severe hypoxaemia (PaO_2 30 to 50 mm Hg), rapid onset of pulmonary edema, mild to moderate hypotension, and fever (defined as a 1°C to 2°C rise in body temperature from pre-transfusion baseline) within 6 hours of receiving a plasma-containing blood transfusion	Goldman 2005

Appendix 4. Components of the red cell storage lesion

Component (Hess 2010)	**Type of lesion storage**
1. Metabolic	1.1. Acidosis 1.2. Lower ATP, DPG 1.3. Lower glutathione, NADH, NADPH

(*Continued*)

2. Enzymatic	2.1. Loss of surface glycands 2.2. Lysolipids 2.3. Protein damage
3. Oxidative	3.1. Damage to proteins 3.2. Decoration of protein 3.3. Oxidised lipids 3.4. Lysolipids
4. Physiologic	4.1. Shape change 4.2. Membrane loss 4.3. Apoptosis

Appendix 5. Search Strategies

Cochrane Injuries Group Specialised Register
#1 ((Blood or Erythrocyt* or Platelet* or Plasma or Component*)) AND ((Transfus* or exchange*)) [REFERENCE] [STANDARD]
#2 (Storage or store* or storing or preserv* or PSL or blood-bank*) OR (blood and bank*) [REFERENCE] [STANDARD]
#3 #1 AND #2 [REFERENCE] [STANDARD]
Cochrane Central Register of Controlled Trials, *The Cochrane Library*
#1 MeSH descriptor Blood Transfusion explode all trees
#2 MeSH descriptor Platelet Transfusion explode all trees
#3 MeSH descriptor Erythrocyte Transfusion explode all trees
#4 MeSH descriptor Blood Component Transfusion explode all trees
#5 MeSH descriptor Exchange Transfusion, Whole Blood explode all trees
#6 (Blood or Erythrocyt* or Platelet* or Plasma or Component*) near3 (Transfus* or exchange*)
#7 transfusion*:ti
#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9 MeSH descriptor Blood Preservation explode all trees
#10 MeSH descriptor Blood Banks explode all trees
#11 MeSH descriptor Preservation, Biological explode all trees
#12 MeSH descriptor Time Factors explode all trees
#13 (prolonged or long* or continued) near3 (Storage or store* or storing or preserv* or PSL or blood?bank*):ti,ab
#14 (Storage or store* or storing or preserv* or PSL or blood?bank*):ti
#15 (#9 OR #10 OR #11 OR #12 OR #13 OR #14)
#16 (#8 AND #15)
Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R)
1. exp Blood Transfusion/
2. exp Platelet Transfusion/
3. exp Erythrocyte Transfusion/
4. exp Blood Component Transfusion/
5. exp Exchange transfusion, whole blood/
6. ((Blood or Erythrocyt* or Platelet* or Plasma or Component*) adj3 (Transfus* or exchange*)).ab,ti.
7. transfusion*.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp Blood Preservation/
10. exp Blood Banks/

11. exp Preservation, Biological/
12. exp Time Factors/
13. ((prolonged or long* or continued) adj3 (Storage or store* or storing or preserv* or PSL or blood?bank*)).ab,ti.
14. (Storage or store* or storing or preserv* or PSL or blood?bank*).ti.
15. 9 or 10 or 11 or 12 or 13 or 14
16. 8 and 15
17. randomi?ed.ab,ti.
18. randomized controlled trial.pt.
19. controlled clinical trial.pt.
20. placebo.ab.
21. clinical trials as topic.sh.
22. randomly.ab.
23. trial.ti.
24. 17 or 18 or 19 or 20 or 21 or 22 or 23
25. (animals not (humans and animals)).sh.
26. 24 not 25
27. 16 and 26

Embase Classic+Embase (OvidSP)

1. exp Blood Transfusion/
2. exp thrombocyte transfusion/
3. exp Erythrocyte Transfusion/
4. exp blood component therapy/
5. exp exchange blood transfusion/
6. ((Blood or Erythrocyt* or Platelet* or Plasma or Component*) adj3 (Transfus* or exchange*)).ab,ti.
7. transfusion*.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp blood storage/
10. exp Blood Banks/
11. (Storage or store* or storing or preserv* or PSL or blood?bank*).ti.
12. ((prolonged or long* or continued) adj3 (Storage or store* or storing or preserv* or PSL or blood?bank*)).ab,ti.
13. exp "preservation and storage"/
14. exp preservation/
15. 9 or 10 or 11 or 12 or 13 or 14
16. 8 and 15
17. exp Randomized Controlled Trial/
18. exp controlled clinical trial/
19. randomi?ed.ab,ti.
20. placebo.ab.
21. *Clinical Trial/
22. randomly.ab.
23. trial.ti.
24. 17 or 18 or 19 or 20 or 21 or 22 or 23
25. exp animal/ not (exp human/ and exp animal/)
26. 24 not 25
27. 16 and 26

CINAHL Plus (EBSCOHost)

S1	(MH ”Blood Transfusion+“) OR (MH ”Blood Component Transfusion+“) OR (MH ”Erythrocyte Transfusion“) OR (MH ”Exchange Transfusion, Whole Blood“) OR (MH ”Platelet Transfusion“)
S2	(Blood or Erythrocyt* or Platelet* or Plasma or Component*) N3 (Transfus* or exchange*)
S3	TI transfusion*
S4	S1 OR S2 OR S3
S5	(MH ”Blood Preservation“) OR (MH ”Blood Conservation+“)
S6	(MH ”Blood Banks+“)
S7	(prolonged or long* or continued) N3 (Storage or store* or storing or preserv* or PSL or blood?bank*)
S8	TI (Storage or store* or storing or preserv* or PSL or blood?bank*)
S9	S5 OR S6 OR S7 OR S8
S10	S4 AND S9
S11	(MH ”Clinical Trials“)
S12	PT clinical trial*
S13	TX clinical N3 trial*
S14	TI ((singl* N3 blind*) or (doubl* N3 blind*) or (trebl* N3 blind*) or (tripl* N3 blind*)) or TI ((singl* N3 mask*) or (doubl* N3 mask*) or (trebl* N3 mask*) or (tripl* N3 mask*)) or AB ((singl* N3 blind*) or (doubl* N3 blind*) or (trebl* N3 blind*)) or AB ((singl* N3 mask*) or (doubl* N3 mask*) or (trebl* N3 mask*) or (tripl* N3 mask*))
S15	TX randomi?ed N3 control* N3 trial*
S16	(MH ”Placebos“)
S17	TX placebo*
S18	(MH ”Random Assignment“)
S19	TX random* N3 allocat*
S20	MH quantitative studies
S21	S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20
S22	S10 AND S21

ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) & Conference Proceedings Citation Index - Science (CPCI-S)

#1	TS=(randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial)
#2	TS=(controlled clinical trial OR controlled trial OR clinical trial OR placebo)
#3	TS=((singl* OR doubl* OR trebl* OR tripl*) SAME (blind* OR mask*))
#4	#3 OR #2 OR #1
#5	TS=(human*)
#6	#5 AND #4
#7	TS=((prolonged or long* or continued) NEAR/3 (Storage or store* or storing or preserv* or PSL or blood?bank*)) OR TI=((Storage or store* or storing or preserv* or PSL or blood?bank*))
#8	TS=(((Blood or Erythrocyt* or Platelet* or Plasma or Component*) NEAR/3 (Transfus* or exchange*)))
#9	#8 AND #7 AND #6

LILACS
tw:((tw:(sangre OR sangue OR blood)) AND (tw:(reserva OR storage OR store OR transfusion OR transfusão OR transfusión)) AND (db:("LILACS") AND type˙of˙study:("clinical˙trials")))
Clinicaltrials.gov
INFLECT EXACT "Interventional" [STUDY-TYPES] AND INFLECT ("transfusion" OR "storage" OR "store") [TITLES] AND ("01/01/2014" : "06/10/2015") [FIRST-RECEIVED-DATE]
WHO Clinical Trials Search Portal
Title: transfusion OR storage OR store OR preservation
Recruitment: ALL
Date of registration 01/01/2014 to 10/06/2015

CONTRIBUTIONS OF AUTHORS

Arturo Martí-Carvajal conceived of the idea for this review and drafted the review, with comments from Daniel Simancas, and Barbra Peña-González.

Arturo Martí-Carvajal acts as guarantor for the review.

DECLARATIONS OF INTEREST

Daniel Simancas: None known.

Barbra Peña-González: None known.

Arturo Martí-Carvajal: None known.

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Academic

- Iberoamerican Cochrane Center, Spain.

Academic

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

To improve the quality of this Cochrane review, we made the following changes to the original protocol.

1. We changed the order of the primary outcomes using GRADE statement (i.e., the most important clinical outcomes were listed first) and we replaced the term 'safety' with 'adverse events'.

2. We conducted trial sequential analysis in order to assess the risk of random errors in cumulative meta-analyses.

3. Our criteria for assessment of statistical heterogeneity in the protocol were to classify an I^2 of 40-60% as moderate, and 75% and above as high. We have corrected this in the review, and moderate is now classified as an I^2 of 50-74%, and 75% or above as high.