Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion (Review)

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[Intervention Review]

Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

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ABSTRACT

Background

Most clinical practice guidelines recommend restrictive red cell transfusion practices, with the goal of minimising exposure to allogeneic blood (from an unrelated donor). The purpose of this review is to compare clinical outcomes in patients randomised to restrictive versus liberal transfusion thresholds (triggers).

Objectives

To examine the evidence for the effect of transfusion thresholds on the use of allogeneic and/or autologous blood, and the evidence for any effect on clinical outcomes.

Search methods

Trials were identified by: computer searches of the Cochrane Central Register of Controlled Trials *(the Cochrane Library* Issue 3, 2009), OVID MEDLINE (1966 to August 2009), Current Contents (1993 to November 2004), and the Web of Science (2004 to August 2009). References in identified trials and review articles were checked and experts contacted to identify any additional trials.

Selection criteria

Controlled trials in which patients were randomised to an intervention group or to a control group. Trials were included where intervention groups were assigned on the basis of a clear transfusion 'trigger', described as a haemoglobin (Hb) or haematocrit (Hct) level below which an RBC transfusion was to be administered.

Data collection and analysis

Relative risks of requiring allogeneic blood transfusion, transfused blood volumes and other clinical outcomes were pooled across trials, using a random effects model. The risk of bias was assessed.

Main results

Seventeen trials involving a total of 3746 patients were identified. Restrictive transfusion strategies reduced the risk of receiving a red blood cell (RBC) transfusion by a relative 37% (RR=0.63; 95% CI 0.54 to 0.74). This equates to an average absolute risk reduction (ARR) of 33% (95% CI 21% to 45%). The volume of RBCs transfused was reduced on average by 0.75 units (95% CI 0.20 to 1.30 units). However, heterogeneity between trials was statistically significant ($P<0.001$; $I^2 \geq 74\%$) for these outcomes. Restrictive transfusion strategies did not appear to impact on the rate of adverse events compared to liberal transfusion strategies (i.e. mortality, cardiac events, myocardial infarction, stroke, pneumonia and thromboembolism). Restrictive transfusion strategies were associated with a statistically significant reduction in the rates of infection (RR=0.76; 95% CI 0.60 to 0.97). The use of restrictive transfusion strategies did not reduce hospital or intensive care length of stay.

Authors' conclusions

The existing evidence supports the use of restrictive transfusion triggers in patients who are free of serious cardiac disease. The effects of conservative transfusion triggers on functional status, morbidity and mortality, particularly in patients with cardiac disease, need to be tested in further large clinical trials. In countries with inadequate screening of donor blood, the data may constitute a stronger basis for avoiding transfusion with allogeneic red cells.

PLAIN LANGUAGE SUMMARY

Safety of blood transfusion improved by the use of 'transfusion thresholds'

Many people are given a transfusion of blood from an unrelated donor as part of their medical treatment. There are, however, risks involved. In particular, infections (including HIV and certain types of hepatitis) may be passed on to the person receiving the blood. This risk is small in high income countries but much larger in poor countries which lack good facilities to test the blood for infections. Because of the risks, doctors try to avoid giving blood unless it is really necessary. One approach is to give the transfusion only if the amount of haemoglobin in the patient's blood has dropped below a certain 'threshold' level. The authors looked for controlled studies evaluating the effectiveness of this approach. They found 17, with a total of 3746 patients. The authors say that more research is needed and that, until more is known, patients who have a serious heart problem should not be treated in this way. The authors conclude that, for most patients, blood transfusion is probably not essential until haemoglobin levels drop below 7.0 grammes per decilitre.

BACKGROUND

Blood is an indispensable product in modern medical practice (Amin 2004). Red blood cells (RBC) are used to improve oxygen delivery to tissues in situations of haemorrhage and anaemia (Napolitano 2009). Red blood cell transfusion constitutes one of the mainstays of therapy in the management of anaemic patients and is one of the few treatments that adequately restore tissue oxygenation when oxygen demand exceeds supply (Wang 2010; Klein 2007). Unfortunately the demand for blood products is frequently far greater than supply. In the United States (US) alone a total of 13.9 million RBC units were transfused to 4.9 million recipients in 2001 (Sullivan 2007). The Global Database on Blood Supply (GDBS), established by the World Health Organization (WHO) in 1997 to address global concerns about the safety and availability of blood for transfusion, showed that 80.7 million blood units were collected globally in 167 countries during 2004-2005 (Takei 2009). In the United Kingdom alone there were approximately 2.8 million whole blood donations and 69,777 apheresis donations during 2000/2001 (Varney 2003). In the case of sub-Saharan Africa, the WHO estimates that approximately 6.65 million units of blood are required per year for the region's population of around 650 million, however only 2 million units of blood are currently collected and transfused (Jayaraman 2010).

In developing countries the frequent use of blood transfusion is often coupled with transfusion services that are not equipped to conduct universal antibody screening. In sub-Saharan Africa the median overall risks of becoming infected with HIV, HBV, and HCV from a blood transfusion have been estimated to be 1.0, 4.3, and 2.5 infections per 1000 units respectively (Jayaraman 2010). Based on WHO annual transfusion projections, transfusion alone would be responsible for 28,595 HBV infections, 16,625 HCV

infections, and 6,650 HIV infections in this population. Data modelling has shown that the risk of acquiring HIV in sub-Saharan Africa can be as high as 13 infections per 1000 donations compared to 1 in 1.5 million units in high income countries (Jayaraman 2010).

In most developed countries with well-regulated blood supplies, the safety of allogeneic red cell transfusion has improved significantly over the past 30 years. This has been primarily due to improvements in donor-blood screening procedures and the implementation of more stringent quality control measures (Klein 2007). It has been estimated that the residual risk of transmission through transfusion of HIV, HCV, and HBV in Canada is 1 per 7.8 million donations, 1 per 2.3 million donations, and 1 per 153,000 donations respectively (O'Brien 2007). Globally, the estimated risks of infection per blood unit range from 1 per 100,000 to 1 per 400,000 for HBV, 1 per 1.6 million to 1 per 3.1 million for HCV, 1 per 1.4 million to 1 per 4.7 million for HIV, and 1 per 500,000 to 1 per 3.0 million for HTLV (Goodnough 2008). Data from seven countries (Germany, France, Switzerland, Italy, Spain, United Kingdom, Canada) from 2000-2005 showed the residual risk of transfusion-transmitted viral infections ranged from 0.22-2.48 per 1 million donations for HIV, 0.05-3.94 per 1 million donations for HCV, and 1.51-9.78 per 1 million donations for HBV (Kitchen 2008).

Blood transfusion services worldwide face an ominous financial challenge. In Canada, the cost of allogeneic blood transfusion has almost doubled from 1994/1995 to 2001/2002. Further comparisons show that there has been a threefold increase in the cost of blood distribution and a twofold increase in the cost of blood collection (Amin 2004). The annual cost of collecting, testing, processing and issuing blood products in the UK during 2000/2001 was estimated to be around £284 million. The total cost to the UK National Health Service attributable to blood transfusion in 2000/2001 was estimated to be £898 million with £613.9 million attributed to in-hospital resource use costs (Varney 2003). The total expenditures of Canadian Blood Services have risen from an annualised total of $422 million in 1998/1999 to $638.8 million in 2001/2002 with the major cost driver being the cost associated with measures used to improve the safety of blood transfusion (Wilson 2003). Based on UK and US transfusion data, the cost of implementing the leukocyte-reduction program in the US was estimated to be between $400 and $672 million per annum (Dzik 2000). In the UK the introduction of universal leukocyte-reduction in 1998 to mitigate the risk of transmitting variant Creutzfeldt-Jakob disease (vCJD) via blood transfusion was estimated to cost the National Health Service (NHS) around £70 million per annum (McClelland 2005). In addition to the existing infectious risks, the threat of new or emerging infection is ever present (Kitchen 2008). The implementation of new and more advanced tests to improve the safety of blood transfusion will place significant pressure on already strained health care budgets. Measures to reduce the burden of blood transfusion costs on health care services are continually being sought.

Historically, the widely accepted clinical standard was to transfuse patients when the haemoglobin level dropped below 10.0g/dL or the haematocrit fell below 30%. This '10/30 rule' was first proposed by Adams and Lundy in 1942 and served as a RBC transfusion trigger for decades (Madjdpour 2005; Wang 2010). However, the 1988 National Institutes of Health Consensus Conference in the United States reported that the evidence did not support a single criterion for transfusion (NIH 1988). Since then, several published guidelines have advised against a single threshold for red cell transfusion, recommending that a range of haemoglobin values between 6.0 and 10.0g/dL can be used, depending on the presence of serious co-morbidity (NHMRC & ASBT 2001; BCTMAG 2003; ASA 2006; AAGBI 2008; NBUGI 2001; Napolitano 2009).

The purpose of the review was to find, appraise and summarise the data from high-quality trials that studied the clinical impact of varying thresholds for transfusion with red cells. We were particularly interested in whether the results of randomised controlled trials gave support to the trend for increasingly conservative red cell transfusion practices; in other words that red cell transfusions can be withheld in some circumstances without harming patients.

OBJECTIVES

To examine the evidence on the effect of transfusion thresholds on the use of red cell transfusions and the evidence for any change in clinical outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials with a concurrent control group. Trials were included if the comparison groups were assigned on the basis of a clear transfusion 'trigger' or 'threshold', described as a haemoglobin or haematocrit level (with or without a specified level of haemodynamic instability) that had to be reached before a red cell transfusion was administered. Control group patients were required to be either transfused with allogeneic and/or autologous red blood cells at higher Hb or Hct levels (transfusion threshold) than the intervention group or transfused in accordance with current transfusion practices, which may not have included a well defined transfusion threshold, but involved liberal rather than restrictive transfusion practices.

Types of participants

Trials of surgical or medical patients, involving adults and/or children were included.

Types of interventions

The intervention considered was the use of transfusion thresholds ('triggers') as a means of guiding allogeneic and/or autologous red blood cell transfusion.

Types of outcome measures

Primary outcomes

- the proportion of patients 'at risk' who were transfused with allogeneic and/or autologous red blood cells, and the amounts of allogeneic and autologous blood transfused.

Secondary outcomes

- morbidity (non-fatal myocardial infarction, cardiac events, pulmonary oedema, stroke, thromboembolism, renal failure, infection, haemorrhage, mental confusion), mortality, haematocrit levels (post-operative/discharge), and length of hospital stay (LOS).

Search methods for identification of studies

Electronic searches

The following databases were searched:

- Cochrane Injuries Group Specialised Register (searched 21 August 2009),
- CENTRAL (*The Cochrane Library* 2009, Issue 3),
- Ovid MEDLINE(R) (1950 to August Week 2, 2009),
- EMBASE (1980 to 2009 Week 33),
- ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (2004 to August 2009),
- ISI Web of Science: Conference Proceedings Citation Index - Science (CPCI-S) (2004 to August 2009),
- Current Contents (1993 to November 2004).

The search strategies are presented in Appendix 1.

Searching other resources

Contact was made with experts in the field to identify reports or projects in progress, relevant to the review. The reference lists of related reviews and identified articles were checked for relevant studies. In addition references in the identified trials were checked and authors contacted, where possible, to identify any additional published or unpublished data.

Data collection and analysis

Selection of studies

The titles and/or abstracts of the electronic search results were screened by two authors (one author, KK, for the 2009 update) to identify trials in which patients were randomised to a restrictive transfusion strategy (transfusion threshold and/or protocol), or to a control group, who were randomised to a liberal transfusion strategy. From the results of the screened electronic searches, bibliographic searches and contacts with experts, two authors (one author for the 2009 update) independently selected trials that met previously defined inclusion criteria. These authors then independently extracted study characteristics and outcomes using an article extraction form. The extraction form recorded information regarding: study type, methodology descriptions, the presence of a transfusion threshold, transfusion protocol, the type of surgery involved, clinical setting, treatment outcomes, and general comments. Articles were examined for inclusion/exclusion criteria by two authors with disagreements resolved by consensus.

Data extraction and management

Articles that met the inclusion criteria were processed for data extraction. Data were then entered into Review Manager by one author. Authors of trials were contacted to provide missing data. A data extraction form was used to record data on the following outcomes; the number of patients exposed to allogeneic blood, the amount of allogeneic blood transfused, the number of patients receiving any transfusion (allogeneic blood, autologous blood, or both). For trials involving surgical patients, the following outcomes were recorded; post-operative complications (infection, haemorrhage, non-fatal myocardial infarction, cardiac events, renal failure, stroke, thromboembolism, pulmonary oedema, mental confusion), mortality, and length of hospital stay (LOS). Data were also be recorded on; blood loss, and, haemoglobin and haematocrit levels (on admission, pre-post transfusion, at discharge). Information regarding, demographics (age, sex), type of surgery or medical condition was also recorded on the data extraction form. Data were extracted for allogeneic blood transfusion if it was expressed as packed red blood cells (RBC). Information regarding the use of fresh frozen plasma (FFP) and /or platelets was documented.

Assessment of risk of bias in included studies

This was assessed by one author using the Cochrane Collaboration's tool for assessing risk of bias presented in Higgins 2008.

The following domains were assessed for each study;

- sequence generation,
- allocation concealment,
- blinding,
- incomplete outcome data.

We completed a risk of bias table for each study, incorporating a description of the study's performance against each of the above domains and our overall judgment of the risk of bias for each entry as follows; 'Yes' indicates low risk of bias 'Unclear' indicates unclear or unknown risk of bias 'No' indicates high risk of bias.

Assessment of heterogeneity

Statistical heterogeneity was examined by both the I^2 and chi^2 tests. The I-squared test describes the percentage of total variation across studies due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity; substantial heterogeneity is considered to exist when I^2>50% (Higgins 2008). For the chi^2 statistic, a P value of <0.10 was used to indicate the presence of statistically significant heterogeneity.

Assessment of reporting biases

Funnel plots were examined for evidence of publication bias.

Data synthesis

All analyses were performed using Review Manager software. Data on the numbers of patients exposed to allogeneic blood and the numbers of patients in each treatment group were entered into Review Manager. The relative risks (RR) for allogeneic blood transfusion in the intervention group as compared with the control group, and the corresponding 95% confidence intervals, were calculated for each trial using the random effects model (Der Simonian 1986). A similar approach was adopted to examine the other outcomes of transfusion. The mean number of units of red blood cells transfused to each group and the corresponding standard deviations were also entered. The mean difference (MD) and 95% confidence intervals (CI) was used to express the average reduction in the number of units of RBC administered to the intervention group, compared with the control. Data in millilitres (mls) were converted to units by dividing by 300.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were performed to explore treatment effects by clinical setting, transfusion threshold and adequacy of allocation concealment.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Included studies

Seventeen eligible studies were identified and are included in this review.

Of the 17 included trials the clinical settings were variable. Eight studies took place within the context of surgery – cardiac, vascular or orthopedic (Bracey 1999; Bush 1997; Carson 1998; Foss 2009; Grover 2005; Johnson 1992; Lotke 1999; So-Osman 2010). Five trials were in the context of acute blood loss and/or trauma (Blair 1986; Colomo 2008; Fortune 1987; Topley 1956; Zygun 2009), three trials involved patients in critical care units (Hebert 1995; Hebert 1999; Lacroix 2007) and one trial involved leukaemia patients undergoing chemotherapy or stem cell transplantation (Webert 2008).

There was considerable variation with regard to the restrictive transfusion strategies used. These varied from 7.0 to 9.0g/dL, with two further trials specifying haematocrit values of 25 or 30% (equivalent to haemoglobin levels of around 8.0 and 10.0g/dL respectively). The liberal transfusion triggers varied from 100% of 'normal red cell volume' (Topley 1956), two units of blood (immediately in one trial (Blair 1986), post-operatively in another (Lotke 1999) irrespective of clinical state; transfusion sufficient to maintain haemoglobin levels at or above 12.0g/dL (Webert 2008), 10.0g/dL (Bush 1997; Carson 1998; Foss 2009; Grover 2005; Hebert 1995; Hebert 1999), 9.5g/dL (Lacroix 2007), and 9.0g/dL (Bracey 1999; Colomo 2008; Zygun 2009); two trials specified the liberal triggers as haematocrit levels of 32% (Johnson 1992) and 40% (Fortune 1987). One trial compared a new uniform, restrictive transfusion policy with more liberal standard care (So-Osman 2010).

In these trials random allocation was at the level of the patient, not the clinician or clinical unit. Consequently, participating clinicians may have been responsible for patients in both arms of the trials. Eight trials included more than 100 patients. A total of 3746 trial participants were included in this systematic review.

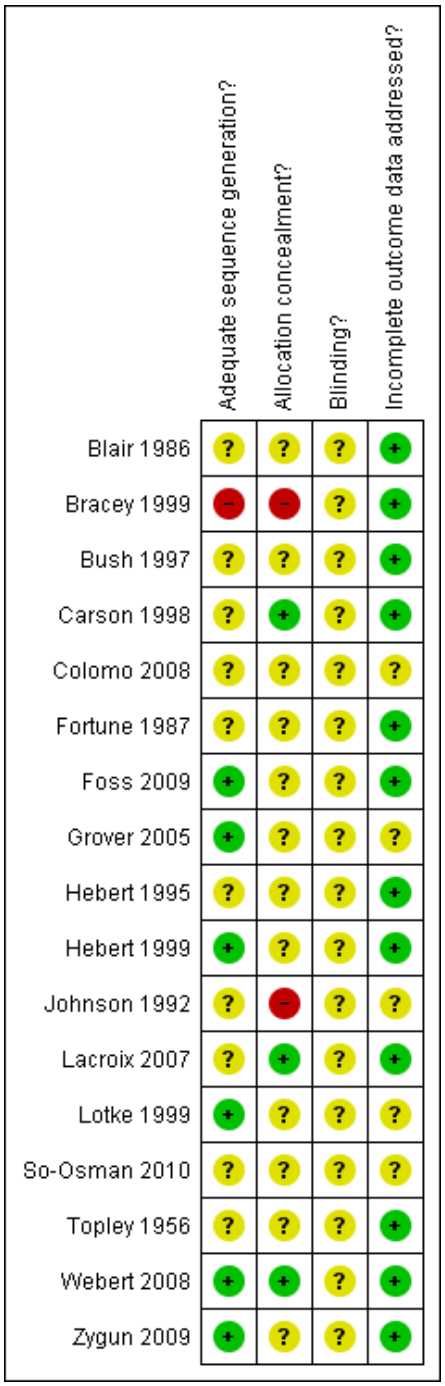
Excluded studies

One randomised controlled trial was confined to patients with sickle cell disease, and was excluded as the trigger was based on the level of HbS, not the haemoglobin or haematocrit level (Vichinsky 1995).

Risk of bias in included studies

For further details regarding the performance of the studies against each domain, please see the 'Risk of bias' tables. A summary of the information in the tables is given below. Additionally, a visual summary of judgements about each methodological quality item for each included trial is shown in Figure 1.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

Adequate sequence generation

The risk of bias for this item was judged to be low for six trials, five of which used computer randomisation and one used a table of random numbers to allocate patients. One trial based allocation on hospital record number and was judged to be at high risk of bias, while the remaining 10 trials presented insufficient information to assess the adequacy of sequence generation and were rated as unclear.

Allocation concealment

The risk of bias for this item was judged to be low for three trials all of which used central allocation. Twelve trials were rated as unclear; six used sealed envelopes however, it was not clear if they were used with appropriate safeguards (e.g. sequentially numbered) to adequately conceal allocation. The other six rated as unclear did not present any information regarding allocation concealment. Two trials were rated as being at high risk of bias for this domain.

Blinding

The nature of the intervention means that blinding of clinicians involved in the care and administration of blood transfusions would not have been feasible, the extent to which this could have biased the results is unclear, thus none of the studies have been rated as being at low risk of bias for this domain. However, blind outcome assessment was reported as being used in six trials.

Incomplete outcome data

Twelve trials were rated as being at low risk of bias for this domain as they either had no missing data or performed intention-to-treat analyses. A small number of exclusions were reported in the remaining five trials although the extent to which this may have introduced bias is uncertain, thus these trials were rated as unclear.

Effects of interventions

Sixteen of the 17 trials presented data suitable for inclusion in the pooled analyses.

Despite the heterogeneity in the methods and transfusion triggers reported in these randomised trials, it was possible to extract and combine data sets from five or more trials for nine outcomes: exposure to red cell transfusion, exposure to red cell transfusion (allogeneic), average volume of red cells transfused in all patients, average volume of red cells transfused in transfused patients, haematocrit levels, cardiac events, myocardial infarction, mortality at 30 days, and length of hospital stay.

Red cell transfusion

Data on the frequency of transfusions were extractable from 15 trials. On average, the implementation of a restrictive transfusion trigger reduced the risk of receiving a red cell transfusion by a relative 37% (RR=0.63; 95% CI 0.54 to 0.74). Heterogeneity between these trials was statistically significant (chi^2=123.82, df=14, P<0.00001; I^2=89%). The quantities of blood transfused were reported in eight trials. The use of a restrictive transfusion trigger resulted in an average saving of 0.75 units of red cells per transfused patient (MD=-0.75; 95% CI -1.30 to -0.20). Heterogeneity between these trials was statistically significant (chi^2=27.05, df=7, P=0.0003; I^2=74%).

Haemoglobin/Haematocrit levels

Post-operative haemoglobin or haematocrit levels were reported for nine trials. However, the timing of measurement varied, being the average measured over a number of days after hospitalisation (or operation) in four trials, a single value prior to discharge in four trials and a single value after the first transfusion in one trial. When data were pooled (without regard to timing, which was consistent within studies), patients assigned to a restrictive strategy had haematocrit levels on average 4.7% (MD= -4.69; 95% CI -6.71 to -2.67) lower than patients assigned to a liberal transfusion strategy. Heterogeneity between these trials was statistically significant (chi^2=463.96, df=8, P<0.00001; I^2=98%).

Mortality

Thirty-day mortality data were reported for nine trials. There was no statistically significant difference in 30-day mortality between restrictive and liberal transfusion strategies (RR=0.83; 95% CI 0.66 to 1.05). Heterogeneity between these trials was not statistically significant (chi^2=5.09, df=7, P=0.65; I^2=0%). It should be noted that one study of patients in intensive care (Hebert 1999) contributed 75% of the weight in the meta-analysis of this outcome.

Hospital length of stay

Seven trials reported data on length of hospital stay. These data indicated that the reduction in red blood cell transfusion was not associated with a prolongation in hospital stay (MD= -0.39 days; 95% CI -0.91 to 0.13 days). Heterogeneity between these trials was not statistically significant (chi^2=1.40, df=6, P=0.97; I^2=0%).

Cardiac events

Five trials reported data on cardiac events. The rates of cardiac events (myocardial infarction, cardiac arrhythmias, cardiac arrest, pulmonary oedema and angina) were not increased significantly by the use of restrictive transfusion strategies (RR=0.76; 95% CI 0.57 to 1.00). Heterogeneity between these trials was not statistically significant (chi²=4.87, df=4, P=0.30; I²=18%).

Myocardial infarction

Seven trials reported data on myocardial infarction. The use of a restrictive transfusion threshold did not appear to impact adversely on the rates of myocardial infarction (RR=0.50; 95% CI 0.21 to 1.21). There was no evidence of statistical heterogeneity between trials (chi²=5.05, df=6, P=0.54; I²=0%).

Infections

Four trials reported data on infections. The rate of infections was decreased by a relative 24% with the use of restrictive transfusion strategies (RR=0.76; 95% CI 0.60 to 0.97). Heterogeneity between these trials was not statistically significant (chi²=2.74, df=3, P=0.43; I²=0%).

Other outcomes

A number of other potentially relevant clinical outcomes were reported in individual trials, including stroke, thromboembolism, multi-organ failure, mental confusion, and delayed wound healing. Although there were no statistically significant differences between restrictive and liberal transfusion strategies for any of these outcomes the overall event rates were low. Interestingly, one trial (Blair 1986) reported a decreased risk of re-bleeding in patients randomised to a restrictive transfusion strategy compared to patients randomised to a liberal transfusion strategy (RR=0.10; 0.01 to 0.75). Where reported, heart rates, cardiac index, and systemic vascular resistance also appeared to be unaffected (Bush 1997; Johnson 1992).

Sensitivity analyses

A post hoc sensitivity analysis was performed to explore the effects of the inclusion of data from the Webert 2008 trial in the pooled analyses. Webert 2008 explored whether a higher transfusion threshold would be beneficial for patients with acute leukaemia, unlike the other included studies which investigated the safety of a lower transfusion threshold. When data from Webert 2008 were excluded from the pooled analysis blood transfusion exposure, the relative risk was reduced slightly from 0.63 (95% CI 0.54 to 0.74) to 0.61 (95% CI 0.53 to 0.71). Heterogeneity between these trials remained statistically significant (chi²=96.82, df=13, P<0.00001; I²=87%).

DISCUSSION

We identified 17 randomised clinical trials evaluating different red cell transfusion triggers carried out over a 55-year time period. These trials enrolled 3746 patients from divergent patient populations. The results of the meta-analyses indicated that, on average, conservative transfusion strategies were associated with a reduction of more than one third in the number of patients receiving blood, a red cell transfusion requirement that was approximately one unit lower, and haematocrit values (average post-operative) that were around 5% lower than in the liberal transfusion group. However, such results need tempering against the significant heterogeneity of the trials assessed.

Sources of heterogeneity

For the main outcomes (the number of patients exposed to blood transfusion, and the amount of blood transfused) substantial heterogeneity was observed. The variation was in terms of the size (but not the direction) of the treatment effect. The individual trials (with five exceptions - Bush 1997, Grover 2005; So-Osman 2010; Topley 1956 and Webert 2008) found that a conservative transfusion trigger statistically significantly reduced the probability of receiving a red cell transfusion with the relative risk estimates ranging from 0.21 to 0.96. However, some confidence intervals were non-overlapping. Heterogeneity might have been anticipated, as the clinical settings and the transfusion triggers differed between trials. In addition, the primary outcome in the meta-analysis — the decision to transfuse — is a practice variable, and involves a degree of subjectivity. It cannot be argued that the treatment effect varied according to the rate of red cell transfusion in the control groups, as most patients (78%) in the liberal transfusion groups received red cell transfusions.

The level of the transfusion trigger between trials does not seem to account for the variation in treatment effect size; the relative risk appeared unrelated to it. However, the degree of difference within trials, between the transfusion triggers of the intervention and control groups may account for some of the variation observed in the treatment effect size. The effect estimates for trials comparing well-defined transfusion rates that differed by 2.0g/dL tended to be larger than the estimates for trials comparing thresholds differing by less than 2.0g/dL. Although these apparent 'associations' may also be due to the play of chance, such observations warrant further discussion.

Two trials (Blair 1986; Lotke 1999) showed greater benefit (in favour of restrictive transfusion strategies) in reducing exposure to red cell transfusion, than any of the other trials. These two trials appeared to be adding considerably to the observed heterogeneity. In Blair 1986 the control group were routinely transfused (as dictated by the trial protocol) at least two units of blood within 24 hours of hospital admission, regardless of their Hb level and clinical state, whereas the intervention group were only transfused

blood when their Hb concentration fell below 8.0g/dL or they displayed signs of shock. For this trial (Blair 1986) the transfusion exposure rate for the intervention group was 19% compared to 100% for the control group. For the trial conducted by Lotke 1999 the control group received all of their pre-operatively donated autologous (PAD) blood (2 units/patient) immediately after surgery (as dictated by the trial protocol) whereas the patients in the intervention group were not transfused their PAD blood unless their Hb concentration fell to less than 9.0g/dL. For this trial (Lotke 1999) the transfusion exposure rate for the intervention group was 26% compared to 100% for the control group.

Five trials (Bush 1997; Grover 2005; So-Osman 2010; Topley 1956; Webert 2008) failed to show a statistically significant reduction in red cell transfusion rates. For Bush 1997 and Webert 2008 protocol violations may have impacted significantly on the rates of transfusion in the intervention groups. In Bush 1997, patients randomised to the intervention group were to be transfused allogeneic red cells, and in some instances autologous red cells, when their Hb concentration fell below 9.0g/dL, the control group were transfused when their Hb concentration fell below 10.0g/dL. The authors of Bush 1997 conceded that not all the patients randomised to the restrictive transfusion strategy reached the transfusion threshold level of Hb <9.0g/dL because they either had minimal intra-operative blood loss or were excessively transfused by the anaesthetists or surgeons. The later may account for the relatively small difference in transfusion rates between the intervention and control groups (88% versus 80%, respectively). In Webert 2008, patients were allocated to receive RBC transfusion when their Hb level fell below 8.0 g/dL in the intervention group or 12.0g/dL in the control. The trial authors note that a number of patients received transfusion before their assigned threshold had been reached; compliance with the assigned threshold was achieved only 64% of the time in the intervention and 70% of the time in the control group. This also may explain the similar transfusion rates observed in the two groups (90% and 94% for the restrictive and liberal groups, respectively). The trial by So-Osman 2010 compared a new age-dependent restrictive transfusion policy with the standard policy used in the three participating hospitals. Deviation from the assigned trigger was not found to be a problem, however differences in the transfusion threshold forming the standard policy of the hospitals may explain the lack of difference observed in transfusion rates (36% and 39% for intervention and control, respectively). The trial by Topley 1956 was designed so that one group of patients ('Under-transfused' group) would have a red cell volume (RCV) of 70-80% of normal at the end of resuscitation, whilst the control group ('Adequately transfused' group) would have a RCV of 100% of normal or over at the end of resuscitation. However, as reported, in practice these objectives were achieved with an accuracy of only ±20%.

The most common and disturbing feature of the trials reviewed here was the high rates of transfusion amongst the control groups. Of the 15 trials that provided data on the proportion of patients transfused blood (allogeneic and/or autologous blood), 11 trials had blood transfusion rates in excess of 88% for the control group. For five of these 11 trials, the control group had red cell transfusion rates of 100%. In summary, these high transfusion rates in the control groups may be explained by the following: (1) clinical setting - eight trials involved trauma or critically ill patients (a subgroup of patients at greater risk of developing anaemia due the nature of their injury or illness); (2) the transfusion threshold used - in the majority of trials the control groups were transfused when their Hb concentration fell below 10.0 g/dL (a relatively high threshold by modern standards); and (3) pre-operatively donated autologous (PAD) blood was used - in one trial (Bush 1997) PAD blood was used in conjunction with allogeneic red cell transfusion, and in two trials (Johnson 1992; Lotke 1999) PAD was used exclusively. There is no evidence to suggest that clinical setting or adequacy of allocation concealment explains the variability in the effect estimates.

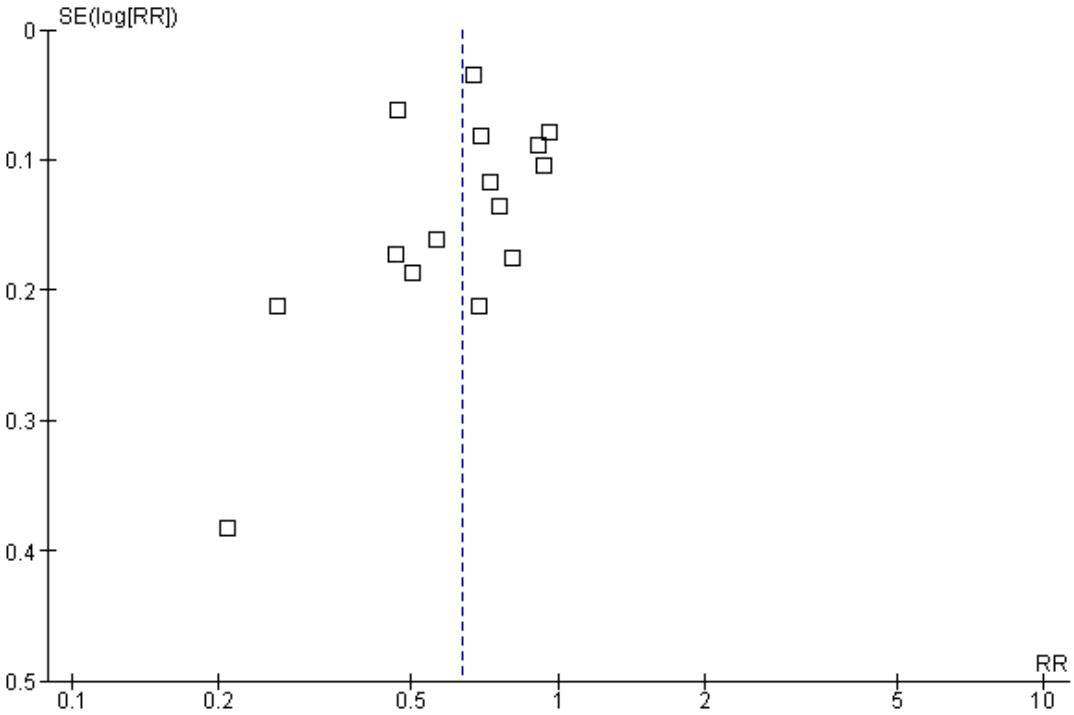
Adverse events and other outcomes

Mortality, cardiac morbidity, and length of hospital stay did not appear to be adversely affected by the lower use of red cell transfusions. Although these data are quite informative, and tend to support the recent move to more restrictive transfusion practices, they are insufficient to address our main research questions, which concerned the benefits and harms associated with different transfusion thresholds, particularly in patients with serious co-existing disease. Although very little heterogeneity was seen for the outcome variable, mortality, the meta-analysis was dominated by one trial (Hebert 1999) that contributed 75% of the statistical information.

Sources of bias

We performed extensive searches in an attempt to identify all eligible trials irrespective of publication status. Despite these efforts, inspection of the funnel plot (Figure 2) suggests the possibility of publication bias or other small study biases affecting the exposure to blood transfusion outcome. Publication bias leading to the exclusion of small studies with non-significant results, may lead to an over-estimate of treatment effect. However, the existence of true heterogeneity should be considered as a potential explanation for the funnel plot asymmetry.

Figure 2. Funnel plot of comparison: 3.1 Patients exposed to blood transfusion (all studies).



Our analyses demonstrate that only one trial (Hebert 1999) was adequately powered to evaluate the impact of different transfusion strategies on mortality and morbidity. Hebert 1999 was the largest study, involving 838 intensive care patients. Given this, the meta-analysis of mortality is dominated by a study of patients in intensive care, and therefore it is uncertain if the results can be applied to other clinical settings.

Several important clinical outcomes have not been evaluated in the trials published to date. We have previously hypothesised that liberal transfusion may improve functional recovery and reduce nursing home placement in elderly hip fracture patients (Carson 1998). Observational data suggest that higher blood counts may be associated with less post-operative delirium (Weiskopf 2000).

This systematic review found minimal evidence of the safety of conservative transfusion triggers in important subsets of patients, including those with severe cardiovascular disease, renal failure, and haematological disorders. The results of two small observational studies, one involving patients with vascular disease (Nelson 1993) and the other involving patients undergoing radical prostatectomy (Hogue 1998), suggest improved outcome with a liberal transfusion trigger. These findings are consistent with animal data (Hagl 1977; Wilkerson 1988; Yoshikawa 1973) and a study in patients who declined blood transfusion for religious reasons, which showed higher mortality in patients with cardiovascular disease than patients without cardiovascular disease as the haemoglobin level fell below 10.0g/dL (Carson 1996). Overall, the rates of cardiac events in this meta-analysis were not increased by the use of conservative transfusion triggers. However, other than one relatively small study in patients having coronary artery bypass surgery, it is unclear how many patients with established cardiac diseases were included in these trials.

Although some guidelines recommend transfusion for symptoms of haemodynamic instability, rather than for a specific trigger haemoglobin level (AAGBI 2008; ASA 2006; NBUGI 2001; NHMRC & ASBT 2001; Napolitano 2009), we found only one small pilot study of 84 patients that evaluated this transfusion strategy (Carson 1998). This study found a non-significant increase in mortality in patients in the symptomatic transfusion group.

The results of these trials need to be viewed against four large observational studies that compared clinical outcomes at varying haemoglobin levels in transfused and non-transfused patients, and found conflicting results. In a study of 2202 patients undergoing coronary bypass surgery, the liberal transfusion group had a higher incidence of myocardial infarction than the conservative transfusion group (Spiess 1998). In a study of 8787 hip fracture patients, there was no difference in short or long-term mortality between patients transfused and not transfused down to a post-

operative haemoglobin of 8.0 g/dL (Carson 1998). In a study of 4470 ICU patients, mortality was reduced in patients receiving transfusion of up to six units of blood (Hebert 1997). A retrospective study of 78,974 Medicare beneficiaries (Wu 2001), found that blood transfusion was associated with a lower short-term mortality rate among elderly patients with acute myocardial infarction if the haematocrit on admission was 30% or lower and that blood transfusion may be effective with a haematocrit as high as 33% on admission. The main limitation of these observational studies is that there may be residual confounding by indication, despite the extensive statistical adjustment of the results. It is possible that differences in patient characteristics between transfused and non-transfused patients may not be identified, or adequately adjusted for. This point is emphasized by the fact that a randomised controlled trial (Hebert 1999) and an observational study (Hebert 1997) in intensive care patients, performed by the same group, came to opposite conclusions. Despite recent assertions to the contrary (Benson 2000; Concato 2000), we believe that adequately powered, rigorously performed, randomised clinical trials are the only way of overcoming these limitations.

A study (Henry 2001a) presented at the Cochrane Colloquium in Lyon, France (9-13 October, 2001), highlighted the significant discrepancies in the results reported by randomised controlled trials compared to those reported by observational studies. This and other studies (Ioannidis 2001) have shown that disagreements in the magnitude of treatment effect between RCTs and observational studies are common. The authors of Henry 2001a analysed the data from studies of various interventions including; pre-operative autologous donation (PAD), acute normovolemic haemodilution, cell salvage, laparoscopic cholecystectomy, hormone replacement therapy, and antioxidant therapy. For PAD alone, the observational studies (n=41) estimate of treatment effect (relative risk), for the number patients exposed to allogeneic blood transfusion, was 0.30 (95% CI 0.26 to 0.35) compared to 0.39 (95% CI 0.27 to 0.57) for the RCTs (n=7). For this intervention (PAD), there appears to be reasonable agreement between the results of the observation studies and the randomised controlled trials. However, the observational studies have appeared to over-estimate the magnitude of treatment effect. Observational studies of the other interventions tended to under-estimate the magnitude of treatment effect. Although the results obtained from well conducted observational studies are extremely valuable, making inferences from observational data sets is problematic, as the sources of error and bias that afflict observational studies do not afflict randomised trials (Henry 2001a).

Conducting randomised clinical trials, where one intervention is a clinical policy regarding red cell transfusion, is demanding. Masking the use of transfusion at the bedside is difficult to achieve unless study personnel are assigned to each patient, an expensive procedure. Outcomes that are determined by observers who are blind to the treatment group is probably the most rigorous approach that is practical. This approach was reported in only six of the trials reviewed here (Carson 1998; Grover 2005; Foss 2009; Johnson 1992; Lotke 1999; Webert 2008). Maintaining the integrity of the randomisation process becomes important if the trial is not to over-estimate the benefit of the intervention (Schulz 1995). Some studies in this review did not report the methods used to conceal the allocation sequence from the treating clinicians. Three trials (Carson 1998; Lacroix 2007; Webert 2008) used a centralised allocation, and four others (Bush 1997; Foss 2009; Hebert 1999; So-Osman 2010) used randomisation codes in sealed envelopes. The latter method has the potential to be unmasked, leading to the potential for selection bias in the inclusion of patients in the trials (Schulz 1995).

The transfusion policies reviewed here represent fairly small modifications to routine clinical practice. They are consistent with the recommendations of published clinical practice guidelines (AAGBI 2008; ASA 2006; BCTMAG 2003; NBUGI 2001; NHMRC & ASBT 2001; Napolitano 2009). The transfusion triggers (in terms of haemoglobin levels) were most often in the range of 8.0 to 9.0g/dL, although values as low as 7.0g/dL were assessed. In fact, the 'restrictive' transfusion triggers in some trials were equivalent to the 'liberal triggers' used in other trials. Nevertheless, the trials documented significant reductions in the rates of red cell transfusion, and worthwhile blood conservation. These effects are similar to what has been documented in meta-analyses of trials of blood sparing techniques, such as cell salvage and anti-fibrinolytic drugs (Carless 2010; Henry 2001b). Adoption of a conservative transfusion threshold appears to be as effective as these technologies in avoiding the need for transfusion, and is likely to cost less. In summary, a conservative transfusion trigger reduces the risk of exposure to red blood cell transfusion and the total number of units transfused. The currently published evidence suggests that conservative transfusion triggers do not adversely affect mortality, cardiac morbidity, or length of hospital stay. Given the uncertain generalisability of the data across different clinical settings, the limited data from patients with underlying cardiovascular disease, and the absence of data on functional recovery, we suggest that additional randomised clinical trials should be undertaken. For the present we recommend the use of a conservative transfusion trigger, but suggest using caution in patients with cardiovascular disease. In countries where there are serious doubts about the safety of donated blood, because of inadequate testing for viral pathogens, the existing data may constitute a stronger basis for avoiding red cell transfusion in many clinical settings.

AUTHORS' CONCLUSIONS

Implications for practice

In patients who do not have advanced coronary artery disease, blood transfusion can probably be withheld in the presence of haemoglobin levels as low as 7.0g/dL so long as there is no notable bleeding. The benefits of minimising allogeneic red cell transfusion

are likely to be greatest where there is doubt about the safety of the blood supply.

Implications for research

Future trials of transfusion 'triggers' should include patients with cardiac and renal disease, and should be large enough to measure the impact that lower thresholds have on clinical outcomes, including functional status.

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REFERENCES

References to studies included in this review

Blair 1986 *{published data only}*
Blair SD, Janvrin SB, McCollum CN, Greenhalgh RM. Effect of early blood transfusion on gastrointestinal haemorrhage. *British Journal of Surgery* 1986;**73**(10):783–5.

Bracey 1999 *{published data only}*
Bracey AW, Radovancevic R, Riggs SA, Houston S, Cozart H, Vaughn WK, Radovancevic B, McAllister HA Jr, Cooley DA. Lowering the hemoglobin threshold for transfusion in coronary artery bypass procedures: effect on patient outcome. *Transfusion* 1999;**39**(10):1070–7.

Bush 1997 *{published data only}*
Bush RL, Pevec WC, Holcroft JW. A prospective, randomized trial limiting perioperative red blood cell transfusions in vascular patients. *American Journal of Surgery* 1997;**174**(2):143–8.

Carson 1998 *{published data only}*
Carson JL, Terrin ML, Barton FB, Aaron R, Greenburg AG, Heck DA, Magaziner J, Merlino FE, Bunce G, Mcclelland B, et al.A pilot randomized trial comparing symptomatic vs. hemoglobin-level-driven red blood cell transfusions following hip fracture. *Transfusion* 1998;**38**(6):522–9.

Colomo 2008 *{published data only}*
Colomo A, Hernandez-Gea V, Muniz-Diaz E, Madoz P, Aracil C, Alvarez-Urturi C, et al.Transfusion strategies in patients with cirrhosis and acute gastrointestinal bleeding. *Hepatology* 2008;**48**(4 (Suppl)):413A.

Fortune 1987 *{published data only}*
Fortune JB, Feustel PJ, Saifi J, Stratton HH, Newell JC, Shah DM. Influence of hematocrit on cardiopulmonary function after acute hemorrhage. *Journal of Trauma* 1987; **27**(3):243–9.

Foss 2009 *{published data only}*
Foss NB, Kristensen MT, Jensen PS, Palm H, Krasheninnikoff M, Kehlet H. The effects of liberal versus restrictive transfusion thresholds on ambulation after hip fracture surgery. *Transfusion* 2009;**49**(2):227–34.

Grover 2005 *{published data only}*
* Grover M, Talwalkar S, Casbard A, Boralessa H, Contreras M, Boralessa H, et al.Silent myocardial ischaemia and haemoglobin concentration: a randomized controlled trial of transfusion strategy in lower limb arthroplasty. *Voz Sanguinis* 2006;**90**:105–12.
Grover M, Talwalker SA, Contreras, Soni N. Blood transfusion threshold and silent myocardial ischemia after lower limb arthroplasty: a randomized controlled trial of transfusion strategy. *Transfusion Alternatives in Transfusion Medicine* 2005;**7**(1 (Suppl)):62–3.

Hebert 1995 *{published data only}*
Hebert PC, Wells G, Marshall J, Martin C, Tweeddale M, Pagliarello G, Blajchman M. Transfusion requirements in critical care. A pilot study. Canadian Critical Care Trials Group [published erratum appears in JAMA 1995 Sep 27; 274(12):944]. *Journal of the American Medical Association* 1995;**273**(18):1439–44.

Hebert 1999 *{published data only}*
* Hebert PC. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *New England Journal of Medicine* 1999;**340**(6):409–17.
McIntyre L, Hebert PC, Wells G, Fergusson D, Marshall J, Yetisir E, Blajchman MJ, Canadian Critical Care Trials Group. Is a restrictive transfusion strategy safe for resuscitated and critically ill trauma patients?. *The Journal of trauma.* 2004;**57**(3):563–8.
McIntyre LA, Fergusson DA, Hutchison JS, Pagliarello G, Marshall JC, Yetisir E, et al.A pilot randomized trial comparing symptomatic vs. hemoglobin-level-driven red blood cell transfusions following hip fracture. *Transfusion* 1998;**38**(6):522–9.

Johnson 1992 *{published data only}*
Johnson RG, Thurer RL, Kruskall MS, Sirois C, Gervino EV, Critchlow J, Weintraub RM. Comparison of two transfusion strategies after elective operations for myocardial revascularization. *Journal of Thoracic & Cardiovascular Surgery* 1992;**104**(2):307–14.

Lacroix 2007 *{published data only}*
Lacroix J, Hébert PC, Hutchison JS, Hume HA, Tucci M, Ducruet T, et al.Transfusion strategies for patients in pediatric intensive care units. *The New England journal of medicine* 2007;**356**(16):1609–19.

Lotke 1999 *{published data only}*
Lotke PA, Barth P, Garino JP, Cook EF. Predonated autologous blood transfusions after total knee arthroplasty:

immediate versus delayed administration. *Journal of Arthroplasty* 1999;**14**(6):647–50.

So-Osman 2010 *{published data only}*
So-Osman C. A restrictive transfusion trigger is a method for blood saving in elective orthopaedic surgery. *Vox Sanguinis* 2004;**87**(Suppl 3):52.
* So-Osman C, Nelissen R, Te Slaa R, Coene L, Brand R, Brand A. A randomized comparison of transfusion triggers in elective orthopaedic surgery using leucocyte-depleted red blood cells. *Vox Sanguinis* 2010;**98**:56–64.

Topley 1956 *{published data only}*
Topley ET, Fisher MR. The illness of trauma. *British Journal of Clinical Practice* 1956;**10**(11):770–6.

Webert 2008 *{published data only}*
Webert KE, Cook RJ, Couban S, Carruthers J, Lee KA, Blajchman MA, et al.A multicenter pilot-randomized controlled trial of the feasibility of an augmented red blood cell transfusion strategy for patients treated with induction chemotherapy for acute leukemia or stem cell transplantation. *Transfusion* 2008;**48**(1):81–91.

Zygun 2009 *{published data only}*
Zygun DA, Nortje J, Hutchinson PJ, Timofeev I, Menon DK, Gupta AK. The effect of red blood cell transfusion on cerebral oxygenation and metabolism after severe traumatic brain injury. *Critical care medicine* 2009;**37**(3):1074–8.

References to studies excluded from this review

Vichinsky 1995 *{published data only}*
Vichinsky EP, Haberkern CM, Neumayr L, Earles AN, Black D, Koshy M, Pegelow C, Abboud M, Ohene-Frempong K, Iyer RV. A comparison of conservative and aggressive transfusion regimens in the perioperative management of sickle cell disease. The Preoperative Transfusion in Sickle Cell Disease Study Group. *New England Journal of Medicine* 1995;**333**(4):206–13.

References to studies awaiting assessment

Slight 2008 *{published data only}*
Slight RD, O'Donohoe P, Fung AKY, Alonzi C, McClelland DBL, Mankad PS. Rationalizing blood transfusion in cardiac surgery: The impact of a red cell volume-based guideline on blood usage and clinical outcome. *Vox Sanguinis* 2008;**95**(3):205–10.

References to ongoing studies

FOCUS *{published data only}*
Carson JL, Terrin ML, Magaziner J, Chaitman BR, Apple FS, Heck DA, Sanders D. Transfusion trigger trial for functional outcomes in cardiovascular patients undergoing surgical hip fracture repair (FOCUS). *Transfusion* 2006;**46**(12):2192–206.

MINT *{published data only}*
Carson JL, Noveck H. Myocardial Ischemia and Transfusion (MINT). ClinicalTrial.gov NCT01167582.

TITRe 2 *{published data only}*
Reeves, B. A multi-centre randomised controlled trial of the effects of a reduction in the threshold for blood transfusion following heart surgery. controlled-trials.com ISRCTN70923932.

Additional references

AAGBI 2008
Association of Anaesthetists of Great Britain and Ireland. Blood Transfusion and the Anaesthetist - Red Cell Transfusion. http://www.aagbi.org/publications/guidelines/docs/red˙cell˙08.pdf. June 2008; Vol. June:1–20.

Amin 2004
Amin M, Fergusson D, Wilson K, Tinmouth A, Aziz A, Coyle D, et al.The societal unit cost of allogenic red blood cells and red blood cell transfusion in Canada. *Transfusion* 2004;**44**(10):1479–86.

ASA 2006
American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Practice guidelines for perioperative blood transfusion and adjuvant therapies. *Anesthesiology* 2006;**105**(1):198–208.

BCTMAG 2003
Guidelines for Red Blood Cell Transfusion. British Columbia Transfusion Medicine Advisory Group. November 2003; Vol. November:1–3.

Benson 2000
Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. *New England Journal of Medicine.* 2000;**342**(25):1878–86.

Carless 2010
Carless PA, Henry DA, Moxey AJ, O'Connell D, Brown T, Fergusson DA. Cell salvage for minimising perioperative allogeneic blood transfusion. *Cochrane Database of Systematic Reviews* 2010;**4**:CD001888. [PUBMED: 20238316]

Carson 1996
Carson JL, Duff A, Poses RM, Berlin JA, Spence RK, Trout R, Noveck H, Strom BL. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. *Lancet* 1996;**348**(9034):1055–60.

Concato 2000
Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *New England Journal of Medicine* 2000;**342**(25):1887–92.

Der Simonian 1986
Der Simonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**:177–88.

Dzik 2000
Dzik S, AuBuchon J, Jeffries L, Kleinman S, Manno C, Murphy MF, et al.Leukocyte reduction of blood components: public policy and new technology. *Transfusion Medicine Reviews* 2000;**14**(1):34–52.

Goodnough 2008
Goodnough LT, Shander A. Risks and complications of blood transfusions: optimizing outcomes for patients with chemotherapy-induced anemia. Advanced Studies in Medicine. 8 2008; Vol. 8, issue 10:357–62.

Hagl 1977
Hagl S, Heimisch W, Meisner H, Erben R, Baum M, Mendler N. The effect of hemodilution on regional myocardial function in the presence of coronary stenosis. *Basic Research in Cardiology* 1977;**72**(4):344–64.

Hebert 1997
Hebert PC, Wells G, Tweeddale M, Martin C, Marshall J, Pham B, Blajchman M, Schweitzer I, Pagliarello G. Does transfusion practice affect mortality in critically ill patients? Transfusion Requirements in Critical Care (TRICC) Investigators and the Canadian Critical Care Trials Group. *American Journal of Respiratory & Critical Care Medicine* 1997;**155**(5):1618–23.

Henry 2001a
Henry DA, Moxey AJ, O'Connell D. Agreement between randomised and non-randomised studies - the effects of bias and confounding. Poster presentation - 9th Cochrane Colloquium, Lyon, France (October 9-13).

Henry 2001b
Henry DA, Moxey AJ, Carless PA, O'Connell D, Mcclelland B, Laupacis A, et al.Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database of Systematic Reviews* 2001, Issue 1. Art. No.: CD001886. DOI: 10.1002/14651858.CD001886.pub2.

Higgins 2008
Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions*. Chicester, UK: John Wiley & Sons, 2008.

Hogue 1998
Hogue CW, Goodnough LT, Monk TG. Perioperative myocardial ischemic episodes are related to hematocrit level in patients undergoing radical prostatectomy. *Transfusion* 1998;**38**(10):924–31.

Ioannidis 2001
Ioannidis JPA, Haidich AB, Pappa M, et al.Comparison of evidence of treatment effects in randomised and nonrandomised studies. *Journal of the American Medical Association* 2001;**286**:821–30.

Jayaraman 2010
Jayaraman S, Chalabi Z, Perel P, Guerriero C, Roberts I. The risk of transfusion-transmitted infections in sub-Saharan Africa. [Review] [40 refs]. *Transfusion* 2010;**50**(2):433–42.

Kitchen 2008
Kitchen AD, Barbara JAJ. Current information on the infectious risks of allogeneic blood transfusion. *Transfusion Alternative in Transfusion Medicine* 2008;**10**:102–11.

Klein 2007
Klein HG, Spahn DR, Carson JL. Red blood cell transfusion in clinical practice. *Lancet* 2007;**370**(9585):415–26.

Madjdpour 2005
Madjdpour C, Spahn DR. Allogeneic red blood cell transfusions: efficacy, risks, alternatives and indications. *British Journal of Anaesthesia* 2005;**95**(1):33–42.

McClelland 2005
McClelland DB, Contreras M. Appropriateness and safety of blood transfusion. *BMJ* 2005;**330**(7483):104–5.

Napolitano 2009
Napolitano LM, Kurek S, Luchette FA, Corwin HL, Barie PS, Tisherman SA, et al.Clinical practice guideline: red blood cell transfusion in adult trauma and critical care. *Critical Care Medicine* 2009;**37**(12):3124–57.

NBUGI 2001
National Blood Users Group Ireland. A Guideline for Transfusion of Red Bllod Cells in Surgical Patients. http://www.dohc.ie/publications/transfusion˙of˙red˙blood˙cells.html. January 2001; Vol. January:1–20.

Nelson 1993
Nelson AH, Fleisher LA, Rosenbaum SH. Relationship between postoperative anemia and cardiac morbidity in high-risk vascular patients in the intensive care unit. *Critical Care Medicine* 1993;**21**(6):860–6.

NHMRC and ASBT 2001
Clinical Practice Guidelines on the Use of Blood Components (red blood cells, platelets, fresh frozen plasma, cryoprecipitate). National Health and Medical Research Council of Australia and the Australasian Society of Blood Transfusion 2001; Vol. September:1–113.

NIH 1988
National Institutes of Health. Perioperative red blood cell transfusion. *Journal of the American Medical Association* 1988;**260**:2700–3.

O'Brien 2007
O'Brien SF, Yi QL, Fan W, Scalia V, Kleinman SH, Vamvakas EC. Current incidence and estimated residual risk of transfusion-transmitted infections in donations made to Canadian Blood Services. *Transfusion* 2007;**47**(2):316–25.

Review Manager
The Nordic Cochrane Centre. Review Manager. 5.0. Copenhagen: The Cochrane Collaboration, 2008.

Schulz 1995
Schulz KF, Chalmers I, Hayes RJ, Altman DJ. Epirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled clinical trials. *Journal of the American Medical Association* 1995;**273**:408–12.

Spiess 1998
Spiess BD, Ley C, Body SC, Siegel LC, Stover EP, Maddi R, D'Ambra M, Jain U, Liu F, Herskowitz A, et al.Hematocrit value on intensive care unit entry influences the frequency of Q-wave myocardial infarction after coronary artery bypass grafting. The Institutions of the Multicenter Study of Perioperative Ischemia (McSPI) Research Group. *Journal of Thoracic & Cardiovascular Surgery* 1998;**116**(3):460–7.

Sullivan 2007
Sullivan MT, Cotten R, Read EJ, Wallace EL. Blood collection and transfusion in the United States in 2001. *Transfusion* 2007;**47**(3):385–94.

Takei 2009
Takei T, Amin NA, Schmid G, Dhingra-Kumar N, Rugg D. Progress in global blood safety for HIV. *Journal of Acquired Immune Deficiency Syndromes: JAIDS* 2009;**52 Suppl 2**: S127–31.

Varney 2003
Varney SJ, Guest JF. The annual cost of blood transfusions in the UK. *Transfusion Medicine* 2003;**13**(4):205–18.

Wang 2010
Wang JK, Klein HG. Red blood cell transfusion in the treatment and management of anaemia: the search for the elusive transfusion trigger. *Vox Sanguinis* 2010;**98**(1):2–11.

Weiskopf 2000
Weiskopf RB, Kramer JH, Viele M, Neumann M, Feiner JR, Watson JJ, Hopf HW, Toy P. Acute severe isovolemic anemia impairs cognitive function and memory in humans. *Anesthesiology* 2000;**92**(6):1646–52.

Wilkerson 1988
Wilkerson DK, Rosen AL, Sehgal LR, Gould SA, Sehgal HL, Moss GS. Limits of cardiac compensation in anemic baboons. *Surgery* 1988;**103**(6):665–70.

Wilson 2003
Wilson K, Hebert PC. The challenge of an increasingly expensive blood system. *CMAJ Canadian Medical Association Journal* 2003;**168**(9):1149–50.

Wu 2001
Wu WC, Rathore SS, Wang Y, et al.Blood transfusion in elderly patients with acute myocardial infarction. *The New England Journal of Medicine.* 2001;**345**(17):1230–6.

Yoshikawa 1973
Yoshikawa H, Powell WJJ, Bland JH, Lowenstein E. Effect of acute anemia on experimental myocardial ischemia. *American Journal of Cardiology* 1973;**32**(5):670–8.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Blair 1986

Methods	Randomised controlled trial.
Participants	50 consecutive patients with severe upper gastrointestinal haemorrhage were randomised to one of two groups: • Liberal group: n = 24; mean (sd) age = 64 (17.6) years • Restrictive group: n = 26; mean (sd) age = 60 (17.8) years
Interventions	• Liberal group received at least 2 units of red blood cells immediately at admission and during their first 24 hours in hospital. • Restrictive group were not transfused red blood cells unless the Hb was less than 8.0g/dL or shock persisted after initial resuscitation with Haemaccel.
Outcomes	***Outcomes reported:*** blood usage (units), re-bleeding, mortality, clotting times, Hct on admission/discharge, kaolin cephalin clotting time after 24 hours, impedance clotting time after 24 hours
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No information reported.
Allocation concealment?	Unclear	No information reported.
Blinding? All outcomes	Unclear	No information reported.
Incomplete outcome data addressed? All outcomes	Yes	No missing data.

Bracey 1999

Methods	Randomised controlled trial.
Participants	428 consecutive patients undergoing elective primary coronary artery bypass graft surgery were randomly assigned to one of two groups: • Liberal group: n = 212; M/F = 82/18; mean (sd) age = 61 (11) years • Restrictive group: n = 216; M/F = 83/17; mean (sd) age = 62 (11) years
Interventions	• Liberal group received transfusions on the instructions of their individual physicians, who considered the clinical assessment of the patient and the institutional guidelines, which propose a Hb level <9.0g/dL as the postoperative threshold for RBC

Bracey 1999 (*Continued*)

	transfusion. • Restrictive group received an RBC transfusion in the postoperative period at a Hb level <8.0g/dL.
Outcomes	***Outcomes reported:*** mortality, length of hospital stay, blood usage (units), blood loss, complications, infection rates, cardiac events
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	Patients were randomly assigned on the basis of the last digit of their medical record number
Allocation concealment?	No	Inadequately concealed (record number).
Blinding? All outcomes	Unclear	No information.
Incomplete outcome data addressed? All outcomes	Yes	Intention-to-treat analysis used. A small numbers of exclusions were reported

Bush 1997

Methods	Randomised controlled trial.
Participants	99 patients undergoing elective aortic or infrainguinal arterial reconstruction were randomised to one of two groups: • Liberal group: n = 49; M/F = 41/8; mean (sd) age = 64 (11) years • Restrictive group: n = 50; M/F = 32/18; mean (sd) age = 66 (10) years
Interventions	• Liberal group had their Hb concentrations maintained at or above 10.0g/dL. • Restrictive group were transfused only when their Hb concentration fell below 9.0g/dL
Outcomes	***Outcomes reported:*** 30-day mortality, length of ICU stay, length of hospital stay, blood use (units), post-operative blood loss, cardiac events, Hct/Hb on admission
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No information.

Bush 1997 (*Continued*)

Allocation concealment?	Unclear	Sealed envelopes were chosen at random for patient assignment
Blinding? All outcomes	Unclear	Both surgeons and anaesthesiologists were informed as to the group of randomisation
Incomplete outcome data addressed? All outcomes	Yes	Appears to be complete.

Carson 1998

Methods	Randomised controlled trial.
Participants	84 hip fracture patients undergoing surgical repair who had postoperative Hb levels <10. 0 g/dL were randomly assigned to one of two groups: • Liberal group: n = 42; M/F = 9/33; mean (sd) age = 81.3 (8.1) years • Restrictive group: n = 42; M/F = 11/31; mean (sd) age = 83.3 (10.8) years
Interventions	• Liberal group received 1 unit of packed RBC at the time of random assignment and as much blood as necessary to keep the Hb level above 10.0g/dL. • Restrictive group received a RBC transfusion for symptoms of anaemia or for a Hb level that dropped below 8.0g/dL.
Outcomes	***Outcomes reported:*** mortality, length of hospital stay, blood usage (units), complications, pneumonia, stroke, thromboembolism
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomisation schedules were stratified by clinical site and cardiovascular disease state. The randomisation was designed in blocks of 2-8 patients to avoid imbalance within a site
Allocation concealment?	Yes	Study personnel at the clinical sites randomly assigned patients by contacting the data coordinating centre's 24-hour automated telephone service
Blinding? All outcomes	Unclear	Blinding of observers.
Incomplete outcome data addressed? All outcomes	Yes	Intention-to-treat analysis used.

Colomo 2008

Methods	Randomised controlled trial.
Participants	214 patients with acute gastrointestinal bleeding and cirrhosis were randomly allocated to one of two groups: • Liberal group: n = 105 • Restrictive group: n = 109 NB: No demographic information were presented, although stated that baseline characteristics were similar in the two groups
Interventions	• Liberal group received packed RBC when Hb level dropped below 9.0g/dL (to maintain Hb concentration at 9.0-10.0 g/dL). • Restrictive group received packed RBC when Hb level dropped below 7.0g/dL (to maintain Hb concentration at 7.0-8.0g/dL).
Outcomes	***Outcomes reported:*** mortality, therapeutic failures, transfusion, Hb concentration, side effects
Notes	Conference abstract.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No information
Allocation concealment?	Unclear	No information
Blinding? All outcomes	Unclear	No information
Incomplete outcome data addressed? All outcomes	Unclear	Insufficient information presented to permit judgement of 'Yes' or 'No'

Fortune 1987

Methods	Randomised controlled trial.
Participants	25 patients were studied prospectively following acute injury and haemorrhage. These patients were randomised to one of two groups: • Liberal group: n = 13; mean age = 46.9 years • Restrictive group: n = 12; mean age = 46.5 years
Interventions	• Liberal group had their Hct brought up to 40% slowly over a period of several hours by the infusion of packed red cells. • Restrictive group had their Hct maintained close to 30% by the appropriate administration of packed red cells. NB: All patients had sustained a Class III or Class IV haemorrhage and had clinical signs of shock (systolic blood pressure <90 torr, heart rate >100bpm, or urine output <20ml/hr) before entry into the study. Patients were resuscitated according to the clinical protocol

Fortune 1987 (*Continued*)

	of the centre first using crystalloid to re-establish organ perfusion and haemodynamic stability and then giving sufficient packed red cells to achieve a Hct close to 30%. Patients were studied twice a day for 3 days after the period of haemorrhagic shock
Outcomes	***Outcomes reported:*** RBC consumption (units), cardiopulmonary parameters: pulmonary capillary wedge pressure (PCWP), Intrapulmonary shunt, Tissue oxygenation / perfusion, Oxygen consumption/delivery, Arterial and venous O_2 saturations, Arterial and venous O_2 contents, Cardiac index (CI), Heart rate, Systemic vascular resistance, Left ventricular stroke work index
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No information.
Allocation concealment?	Unclear	No information.
Blinding? All outcomes	Unclear	No information.
Incomplete outcome data addressed? All outcomes	Yes	Appears to have been complete.

Foss 2009

Methods	Randomised controlled trial.
Participants	120 hip fracture patients were randomly allocated to one of two groups: • Liberal group: n = 60; M/F = 14/46; mean (sd) age = 81 (6.8) years • Restrictive group: n = 60; M/F = 14/46; mean (sd) age = 81 (7.3) years
Interventions	• Liberal group received packed RBC when Hb level dropped below 10.0g/dL. • Restrictive group received packed RBC when Hb level dropped below 8.0g/dL.
Outcomes	***Outcomes reported:*** ambulatory capacity, mortality, length of stay, cardiac complications, infectious complication
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated list.

Allocation concealment?	Unclear	Sealed envelopes.
Blinding? All outcomes	Unclear	Reported as being double-blind.
Incomplete outcome data addressed? All outcomes	Yes	Intention-to-treat analysis used.

Grover 2005

Methods	Randomised controlled trial.
Participants	260 patients undergoing elective lower limb joint replacement surgery were randomly allocated to one of two groups: • Liberal group: n = 109; M/F = 55/54; mean (sd) age = 71.5 (7.6) years • Restrictive group: n = 109; M/F = 48/61; mean (sd) age = 70.7 (7.1) years
Interventions	• Liberal group received packed RBC when Hb level dropped below 10.0g/dL, and Hb concentration maintained between 10.0-12.0 g/dL. • Restrictive group received packed RBC when Hb level dropped below 8.0g/dL and Hb concentration maintained between 8.0-9.5 g/dL.
Outcomes	***Outcomes reported:*** ischaemic load, blood load, Hb concentration, number of units transfused, length of hospital stay, adverse events, new infections requiring antibiotic therapy
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Random numbers table.
Allocation concealment?	Unclear	Sealed envelopes.
Blinding? All outcomes	Unclear	Anaesthetists and surgical team responsible for treatment were aware of allocation. Outcome assessment was blind
Incomplete outcome data addressed? All outcomes	Unclear	Of a recruited 260 patients, outcome data presented for 218. Missing 42 did not have analysable tape recordings

Hebert 1995

Methods	Randomised controlled trial.
Participants	69 normovolaemic critically ill patients admitted to one of five tertiary level intensive care units with Hb values <9.0g/dL within 72 hours of admission were randomly assigned to one of two groups: • Liberal group: n = 36; M/F = 19/17; mean (sd) age = 59 (21) years • Restrictive group: n = 33; M/F = 14/19; mean (sd) age = 58 (15) years
Interventions	• Liberal group were transfused RBC if the Hb level fell to between 10.0-10.5 g/dL. Hb level maintained between 10.0-12.0 g/dL. • Restrictive group were transfused RBC if the Hb level fell to between 7.0-7.5 g/dL. Hb level was maintained between 7.0-9.0 g/dL.
Outcomes	***Outcomes reported:*** mortality, length of hospital stay, length of ICU stay, blood usage (units), complications, Hb levels
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Patients were assigned to one of two groups by consecutive allocation from a random listing stratified by centre and disease severity
Allocation concealment?	Unclear	No information.
Blinding? All outcomes	Unclear	"Blinding of treatment allocation was not feasible".
Incomplete outcome data addressed? All outcomes	Yes	Intention-to-treat analysis used.

Hebert 1999

Methods	Randomised controlled trial.
Participants	838 critically ill patients with euvolemia after initial treatment who had Hb concentrations <9.0g/dL within 72 hours after admission to the intensive care unit were randomly assigned to one of two groups: • Liberal group: n = 420; M/F = 255/165; mean (sd) age = 58.1 (18.3) years • Restrictive group: n = 418; M/F = 269/149; mean (sd) age = 57.1 (18.1) years
Interventions	• Liberal group were transfused RBC when the Hb concentration fell below 10.0g/dL. The Hb concentration was maintained between 10.0-12.0g/dL. • Restrictive group were transfused RBC if the Hb concentration dropped below 7.0g/dL. The Hb concentration was maintained between 7.0-9.0g/dL.

Hebert 1999 (*Continued*)

Outcomes	***Outcomes reported:*** mortality, length of hospital stay, length of ICU stay, blood usage (units), complications, infection rates, cardiac events, pulmonary oedema, pneumonia
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random order.
Allocation concealment?	Unclear	Sealed, opaque envelopes prepared by the data-coordinating centre and distributed to each participating institution where they were opened up sequentially to determine the patients treatment assignment. The envelopes were returned periodically to the coordinating centre for auditing
Blinding? All outcomes	Unclear	"It was not feasible to mask the assigned transfusion strategy from health care providers"
Incomplete outcome data addressed? All outcomes	Yes	Intention-to-treat analysis used.

Johnson 1992

Methods	Randomised controlled trial.
Participants	39 autologous blood donors undergoing elective myocardial revascularisation were randomised to one of two groups: • Liberal group: n = 18; M/F = 16/2; mean (sd) age = 60.5 (6.9) years • Restrictive group: n = 20; M = 20; mean (sd) age = 58.2 (7.5) years
Interventions	• Liberal group received blood to achieve a Hct value of 32%. • Restrictive (conservative) group received transfusions for a Hct value less than 25%. NB: Operative management included sequestration of one or more units of fresh autologous blood in patients with a Hct value greater than 35% who were haemodynamically stable after anaesthetic induction. Red cell conservation was practiced through salvage of oxygenator contents and reinfusion of postoperatively shed mediastinal blood. On the 5th postoperative day all patients were asked to complete an exercise treadmill test. A second test was performed the following day
Outcomes	***Outcomes reported:*** cardiac events, complications, post-operative blood loss, blood use (total units), allogeneic blood use (units), autologous blood use (units), all product blood use (units), number of patients receiving transfusions, mean cardiac index, mean systemic resistance, exercise capacity, Hct levels, length of ICU stay, length of hospital stay

Johnson 1992 (*Continued*)

Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Randomised with the aid of a table of random numbers and an odd-even designation
Allocation concealment?	No	Inadequately concealed.
Blinding? All outcomes	Unclear	Surgeons and anaesthesiologists were blinded as to the group of randomisation until the patient reached the intensive care unit (ICU)
Incomplete outcome data addressed? All outcomes	Unclear	A small number of exclusions were reported.

Lacroix 2007

Methods	Randomised controlled trial.
Participants	637 stable, critically ill children with Hb concentrations below 9.5g/dL within 7 days after admission to an ICU were randomly allocated to one of two groups: • Liberal group: n = 317; M/F = 191/126; mean (sd) age = 39.6 (51.9) months • Restrictive group: n = 320; M/F = 190/130; mean (sd) age = 35.8 (46.2) months
Interventions	• Liberal group were transfused RBC when the Hb concentration fell below 9.5g/dL, with a target range of 11.0-12.0g/dL. • Restrictive group were transfused RBC if the Hb concentration dropped below 7.0g/dL, with a target range of 8.5-9.5g/dL.
Outcomes	***Outcomes reported:*** 28-day mortality, sepsis, transfusion reactions, infections, length of stay
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No information.
Allocation concealment?	Yes	Internet-based, central allocation.
Blinding? All outcomes	Unclear	Clinical staff and parents of the patients were aware of the assignments to study groups, but the statistician and members of the data and safety monitoring committee

		were unaware of the assignments
Incomplete outcome data addressed? All outcomes	Yes	Intention-to-treat analysis used.

Lotke 1999

Methods	Randomised controlled trial.
Participants	152 patients undergoing primary total knee arthroplasty (TKA) were randomly assigned to one of two groups: • Liberal group: n = 65; M/F = 19/46; mean age = 69.7 years • Restrictive group: n = 62; M/F = 20/42; mean age = 68.7 years
Interventions	• Liberal group were transfused autologous blood immediately after TKA, beginning in the recovery room postoperatively. • Restrictive group were transfused autologous blood when the Hb level had fallen to <9.0g/dL.
Outcomes	***Outcomes reported:*** complications, cardiac events, Hb levels, blood usage (units), mental confusion, lethargy, orthostatic hypotension, number of patients transfused
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer random number generator.
Allocation concealment?	Unclear	Not reported.
Blinding? All outcomes	Unclear	Assessments were made by a person blind to the group to which the patient was assigned
Incomplete outcome data addressed? All outcomes	Unclear	Appears to have been complete.

So-Osman 2010

Methods	Randomised controlled trial.
Participants	619, patients undergoing elective orthopaedic hip/knee replacement surgery were randomised to one of two groups: • Liberal (Standard care) group: n = 304; M/F = 118/186; mean (sd) age = 70.3 (9.7) years • Restrictive (New transfusion policy) group: n = 299; M/F = 84/215; mean (sd) age = 70.7 (10.2) years

Interventions	• Liberal group received standard care. • Restrictive group were treated using a 'New transfusion policy'.
Outcomes	***Outcomes reported:*** red blood cell usage, length of hospital stay, Hb levels, mobilisation delay, post-operative complications
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No information.
Allocation concealment?	Unclear	Sealed opaque envelopes.
Blinding? All outcomes	Unclear	Clinicians caring for the patients were aware of allocation status, however, the study investigators were not
Incomplete outcome data addressed? All outcomes	Unclear	Intention-to-treat analysis was not performed, although unclear if this would has biased the results

Topley 1956

Methods	Randomised controlled trial.
Participants	22 trauma patients were randomly allocated to one of two groups: • Liberal group: n = 10 • Restrictive group: n = 12 NB: No demographic data were reported.
Interventions	• Liberal group: the aim was to achieve 100 per cent or more of the red cell volume at the end of resuscitation. • Restrictive group: an attempt was made to leave the red cell volume at the end of resuscitation at 70-80 percent of normal.
Outcomes	***Outcomes reported:*** blood usage (units), blood loss, wound healing, elevated temperature, number of patients transfused, Hb levels
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	When the patient was considered eligible for the trial, they were placed in a severity grade and an envelope

Topley 1956 (*Continued*)

		opened to decide which transfusion schedule was to be used
Allocation concealment?	Unclear	Sealed envelopes.
Blinding? All outcomes	Unclear	No information.
Incomplete outcome data addressed? All outcomes	Yes	Appears to be complete.

Webert 2008

Methods	Randomised controlled trial.
Participants	60 adult patients with acute leukaemia were randomly allocated to one of two groups: • Liberal group: n = 31; M/F = 14/17; mean (sd) age = 45.3 (16.8) years • Restrictive group: n = 29; M/F = 1811; mean (sd) age = 50.8 (15.3) years
Interventions	• Liberal group were transfused two units of RBC when the Hb concentration fell below 12.0g/dL. • Restrictive group were transfused two units of RBC if the Hb concentration dropped below 8.0g/dL, with a target range of 85-95g/dL.
Outcomes	***Outcomes reported:*** transfusions, bleeding risk.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated sequence generation.
Allocation concealment?	Yes	Internet-based, central allocation.
Blinding? All outcomes	Unclear	"Single-blinded" - blind outcome assessment.
Incomplete outcome data addressed? All outcomes	Yes	No missing data.

Zygun 2009

Methods	Randomised controlled trial.
Participants	30 patients with severe traumatic brain injury were randomly allocated to one of three groups: • Liberal group 1: n = 10 • Liberal group 2: n = 10 • Restrictive group: n = 10 NB: Mean (sd) age = 39 (15) years, 70% of trial subjects were male
Interventions	• Liberal group 1 were transfused two units of RBC when the Hb concentration fell below 9.0g/dL. • Liberal group 2 were transfused two units of RBC when the Hb concentration fell below 10.0g/dL. • Restrictive group were transfused two units of RBC if the Hb concentration dropped below 8.0g/dL
Outcomes	***Outcomes reported:*** change in brain tissue oxygen, brain pH, mortality.
Notes	Additional data were obtained from lead trialist for inclusion in the meta-analysis. Data from liberal groups 1 and 2 combined for analysis

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer random number generator.
Allocation concealment?	Unclear	No information.
Blinding? All outcomes	Unclear	No information.
Incomplete outcome data addressed? All outcomes	Yes	No missing data.

Hb = Haemoglobin
Hct = Haematocrit
PCWP = Pulmonary capillary wedge pressure
RBC = Red Blood Cells

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

Study	Reason for exclusion
Vichinsky 1995	Intervention not relevant.

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

FOCUS

Trial name or title	The Transfusion Trial doe Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS)
Methods	Randomised, unblinded, parallel, two-group multi-centre trial
Participants	Patients 50 years or older, who are undergoing surgical repair of a hip fracture, with Hb concentrations below 10.0g/dL within three days after surgery and who have clinical evidence for cardiovascular disease or cardiovascular risk factors Sample size = 2016
Interventions	• Liberal group - receive packed RBC when haemoglobin level dropped below 10.0g/dL. • Restrictive ('symptomatic strategy') group - receive transfusion if develop symptoms of anaemia or if Hb falls below 8.0g/dL
Outcomes	Primary outcome is inability to walk 10 feet (or across a room) without human assistance or death prior to closure of the window for the 60-day, 30 and 60 day mortality. Other outcomes are Hb concentration, acute coronary syndrome (ACS), in-hospital myocardial infarction, unstable angina, or death, disposition on discharge, survival, functional measures, falls, fatigue, pain, readmission to hospital, and self-efficacy, pneumonia, wound infection, thromboembolism, stroke or transient ischaemic attack
Starting date	August 10, 2004
Contact information	Jeffrey Carson (carson@umdnj.edu)
Notes	

MINT

Trial name or title	Myocardial Ischemia and Transfusion
Methods	Randomised, single-blinded, parallel trial
Participants	Anaemic patients with acute coronary syndrome, aged 18 years or over Estimated sample size = 200

MINT (*Continued*)

Interventions	• Liberal group - receive one unit of packed RBC following randomisation and received enough blood to raise Hb concentration above 10g/dL, during hospitalisation for up to 30 days. • Restrictive group - receive transfusion if develop symptoms of anaemia or if Hb falls below 8.0g/dL.
Outcomes	Trial performance and feasibility, Hb concentration, mortality or myocardial ischaemia, unscheduled hospital admission, stroke, congestive hear failure, stent thrombosis, deep vein thrombosis, pulmonary embolism, pneumonia, blood stream infection
Starting date	September 2009
Contact information	Jeffrey Carson (carson@umdnj.edu)
Notes	

TITRe 2

Trial name or title	A multi-centre randomised controlled trial of Transfusion Indication Threshold Reduction on transfusion rates, morbidity and healthcare resources use following cardiac surgery
Methods	Multicentre randomised controlled trial.
Participants	Patients aged 16 year and over undergoing cardiac surgery.
Interventions	• Liberal group - receive packed RBC if Hb concentration falls below 9g/dL, objective is to maintain Hb above 9g/dL. • Restrictive group - receive packed RBC if Hb concentration falls below 7.5g/dL, objective is to maintain Hb above 7.5g/dL.
Outcomes	Infectious events, ischaemic events, units of RBC transfused, duration of hospital stay, all-cause mortality, resource use
Starting date	December 2008
Contact information	
Notes	

DATA AND ANALYSES

Comparison 1. Blood transfusions

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patients exposed to blood transfusion (all studies)	15	3607	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.54, 0.74]
2 Patients exposed to allogeneic blood transfusion	8	1628	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.51, 0.76]
3 Patients exposed to autologous blood transfusion	2	165	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.12, 1.82]
4 Patients exposed to blood transfusion (by clinical setting)	15	3607	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.54, 0.74]
4.1 Cardiac surgery	2	466	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.62, 0.88]
4.2 Orthopaedic surgery	5	1152	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.35, 0.85]
4.3 Vascular	1	99	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.77, 1.08]
4.4 Acute blood loss/trauma	3	286	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.30, 0.89]
4.5 Cancer	1	60	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.82, 1.12]
4.6 Critical care	3	1544	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.42, 0.75]
5 Patients exposed to blood transfusion (by transfusion threshold)	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Difference ≥2g/dL	8	2240	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.52, 0.76]
5.2 Difference <2g/dL	2	527	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.63, 1.07]
6 Patients exposed to blood transfusion (by allocation concealment)	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Low risk of bias	3	781	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.33, 1.09]
6.2 Unclear risk of bias	10	2360	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.53, 0.75]
6.3 High risk of bias	2	466	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.62, 0.88]
7 Units of blood transfused	8	2715	Mean Difference (IV, Random, 95% CI)	-1.19 [-1.85, -0.53]
8 Units of blood transfused in those transfused	8	1555	Mean Difference (IV, Random, 95% CI)	-0.75 [-1.30, -0.20]

Comparison 2. Haematocrit levels

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Haematocrit levels - restrictive versus liberal	9	2574	Mean Difference (IV, Random, 95% CI)	-4.69 [-6.71, -2.67]

Comparison 3. Mortality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ≤14-day mortality	2	821	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.06, 2.96]
2 30-day mortality	9	2461	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.66, 1.05]
3 60-day mortality	2	922	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.46, 2.60]
4 120-day mortality	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5 Hospital mortality	4	1409	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.62, 0.98]
6 ICU mortality	3	736	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.59, 2.23]
7 Mortality (unspecified follow-up period)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Comparison 4. Length of stay

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hospital length of stay	7	2210	Mean Difference (IV, Random, 95% CI)	-0.39 [-0.91, 0.13]
2 ICU length of stay	4	1612	Mean Difference (IV, Random, 95% CI)	-0.32 [-1.09, 0.44]

Comparison 5. Adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cardiac events	5	1530	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.57, 1.00]
2 Myocardial infarction	7	1868	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.21, 1.21]
3 Pulmonary oedema	4	1633	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.18, 1.31]
4 Cerebrovascular accident (CVA) - stroke	3	242	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.17, 5.52]
5 Pneumonia	4	1679	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.78, 1.29]
6 Thromboembolism	2	204	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.14, 6.36]
7 Rebleeding	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8 Infection	4	1788	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.60, 0.97]
9 Renal failure	2	1065	Risk Ratio (M-H, Random, 95% CI)	1.86 [0.66, 5.22]
10 Mental confusion	2	247	Risk Ratio (M-H, Random, 95% CI)	1.86 [0.63, 5.44]

Analysis 1.1. Comparison 1 Blood transfusions, Outcome 1 Patients exposed to blood transfusion (all studies).

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 1 Blood transfusions

Outcome: 1 Patients exposed to blood transfusion (all studies)

Study or subgroup	Restrictive n/N	Liberal n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Blair 1986	5/26	24/24		2.9 %	0.21 [0.10, 0.44]
Bracey 1999	74/212	104/216		7.3 %	0.72 [0.58, 0.91]
Bush 1997	40/50	43/49		7.8 %	0.91 [0.77, 1.08]
Carson 1998	19/42	41/42		6.1 %	0.46 [0.33, 0.65]
Colomo 2008	68/109	95/105		7.9 %	0.69 [0.59, 0.81]
Foss 2009	22/60	44/60		5.8 %	0.50 [0.35, 0.72]
Grover 2005	37/109	46/109		6.1 %	0.80 [0.57, 1.13]
Hebert 1995	18/33	35/36		6.4 %	0.56 [0.41, 0.77]
Hebert 1999	280/418	420/420		8.5 %	0.67 [0.63, 0.72]
Johnson 1992	15/20	18/18		6.9 %	0.76 [0.58, 0.99]
Lacroix 2007	146/320	310/317		8.2 %	0.47 [0.41, 0.53]
Lotke 1999	16/62	65/65		5.3 %	0.26 [0.17, 0.40]
So-Osman 2010	109/299	119/304		7.5 %	0.93 [0.76, 1.14]
Topley 1956	8/12	10/10		5.3 %	0.68 [0.45, 1.04]
Webert 2008	26/29	29/31		8.0 %	0.96 [0.82, 1.12]
Total (95% CI)	**1801**	**1806**		**100.0 %**	**0.63 [0.54, 0.74]**

Total events: 883 (Restrictive), 1403 (Liberal)

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 123.82$, df = 14 ($P<0.00001$); $I^2 = 89\%$

Test for overall effect: $Z = 5.79$ ($P < 0.00001$)

Analysis 1.2. Comparison 1 Blood transfusions, Outcome 2 Patients exposed to allogeneic blood transfusion.

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 1 Blood transfusions

Outcome: 2 Patients exposed to allogeneic blood transfusion

Study or subgroup	Restrictive n/N	Liberal n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Blair 1986	5/26	24/24		5.2 %	0.21 [0.10, 0.44]
Bracey 1999	74/212	104/216		16.7 %	0.72 [0.58, 0.91]
Bush 1997	40/50	43/49		18.5 %	0.91 [0.77, 1.08]
Carson 1998	19/42	41/42		13.2 %	0.46 [0.33, 0.65]
Hebert 1995	18/33	35/36		13.8 %	0.56 [0.41, 0.77]
Hebert 1999	280/418	420/420		21.1 %	0.67 [0.63, 0.72]
Johnson 1992	0/20	3/18		0.4 %	0.13 [0.01, 2.34]
Topley 1956	8/12	10/10		11.0 %	0.68 [0.45, 1.04]
Total (95% CI)	**813**	**815**		**100.0 %**	**0.63 [0.51, 0.76]**

Total events: 444 (Restrictive), 680 (Liberal)

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 30.26$, df = 7 (P = 0.00008); $I^2 = 77\%$

Test for overall effect: Z = 4.69 (P < 0.00001)

Analysis 1.3. Comparison 1 Blood transfusions, Outcome 3 Patients exposed to autologous blood transfusion.

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 1 Blood transfusions

Outcome: 3 Patients exposed to autologous blood transfusion

Study or subgroup	Restrictive n/N	Liberal n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Johnson 1992	15/20	17/18		50.6 %	0.79 [0.60, 1.05]
Lotke 1999	16/62	65/65		49.4 %	0.26 [0.17, 0.40]
Total (95% CI)	**82**	**83**		**100.0 %**	**0.46 [0.12, 1.82]**

Total events: 31 (Restrictive), 82 (Liberal)

Heterogeneity: $Tau^2 = 0.95$; $Chi^2 = 30.25$, df = 1 (P<0.00001); I^2 =97%

Test for overall effect: Z = 1.11 (P = 0.27)

Analysis 1.4. Comparison 1 Blood transfusions, Outcome 4 Patients exposed to blood transfusion (by clinical setting).

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 1 Blood transfusions

Outcome: 4 Patients exposed to blood transfusion (by clinical setting)

Study or subgroup	Restrictive n/N	Liberal n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Cardiac surgery					
Bracey 1999	74/212	104/216		7.3 %	0.72 [0.58, 0.91]
Johnson 1992	15/20	18/18		6.9 %	0.76 [0.58, 0.99]
Subtotal (95% CI)	**232**	**234**		**14.2 %**	**0.74 [0.62, 0.88]**
Total events: 89 (Restrictive), 122 (Liberal)					
Heterogeneity: Tau² = 0.0; Chi² = 0.08, df = 1 (P = 0.78); I² =0.0%					
Test for overall effect: Z = 3.41 (P = 0.00065)					
2 Orthopaedic surgery					
Carson 1998	19/42	41/42		6.1 %	0.46 [0.33, 0.65]
Foss 2009	22/60	44/60		5.8 %	0.50 [0.35, 0.72]
Grover 2005	37/109	46/109		6.1 %	0.80 [0.57, 1.13]
Lotke 1999	16/62	65/65		5.3 %	0.26 [0.17, 0.40]
So-Osman 2010	109/299	119/304		7.5 %	0.93 [0.76, 1.14]
Subtotal (95% CI)	**572**	**580**		**30.9 %**	**0.55 [0.35, 0.85]**
Total events: 203 (Restrictive), 315 (Liberal)					
Heterogeneity: Tau² = 0.22; Chi² = 37.29, df = 4 (P<0.00001); I² =89%					
Test for overall effect: Z = 2.69 (P = 0.0071)					
3 Vascular					
Bush 1997	40/50	43/49		7.8 %	0.91 [0.77, 1.08]
Subtotal (95% CI)	**50**	**49**		**7.8 %**	**0.91 [0.77, 1.08]**
Total events: 40 (Restrictive), 43 (Liberal)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.04 (P = 0.30)					
4 Acute blood loss/trauma					
Blair 1986	5/26	24/24		2.9 %	0.21 [0.10, 0.44]
Colomo 2008	68/109	95/105		7.9 %	0.69 [0.59, 0.81]
Topley 1956	8/12	10/10		5.3 %	0.68 [0.45, 1.04]
Subtotal (95% CI)	**147**	**139**		**16.1 %**	**0.52 [0.30, 0.89]**
Total events: 81 (Restrictive), 129 (Liberal)					
Heterogeneity: Tau² = 0.18; Chi² = 11.22, df = 2 (P = 0.004); I² =82%					

(*Continued* . . .)

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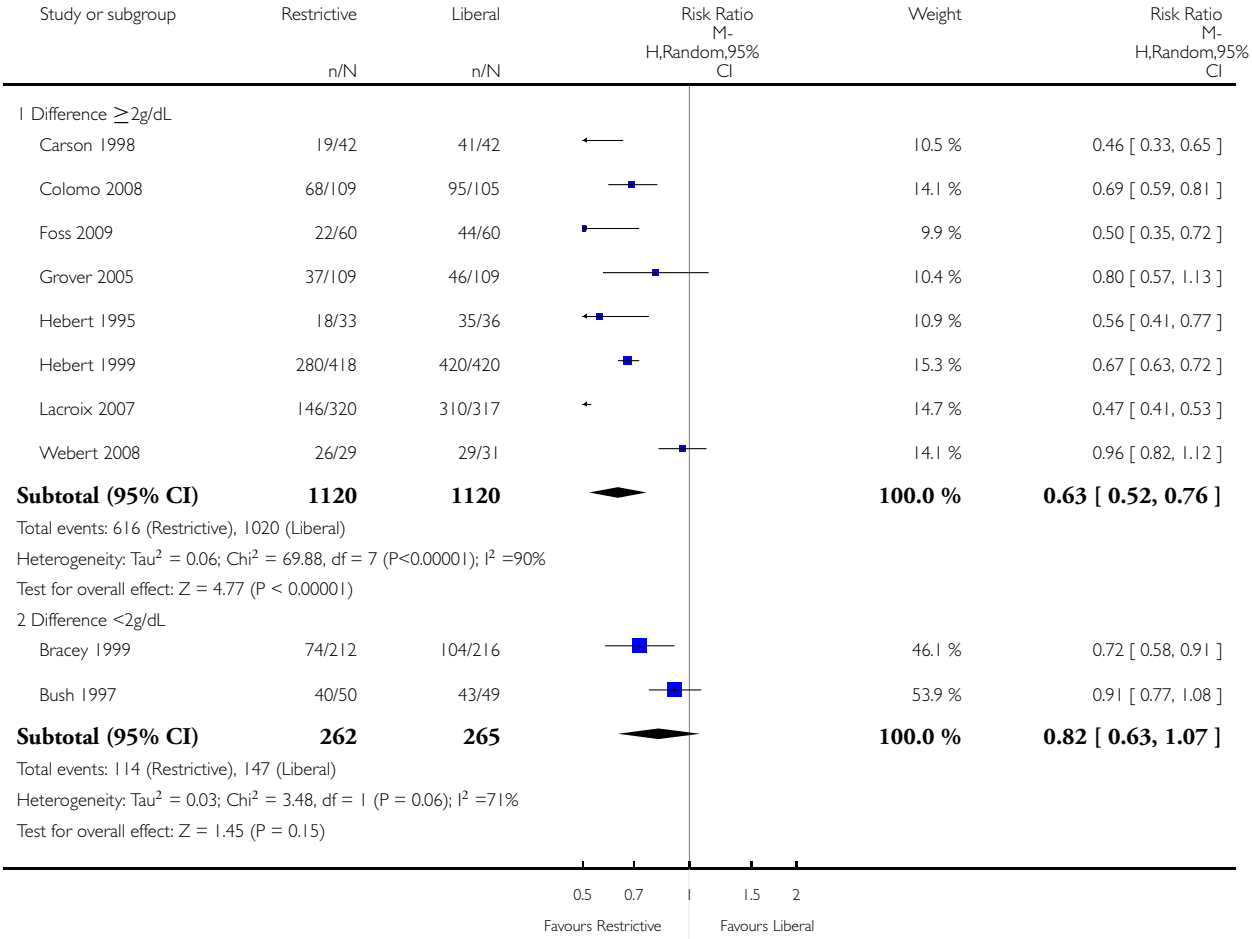
Study or subgroup	Restrictive n/N	Liberal n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 2.36 (P = 0.018)					
5 Cancer					
Webert 2008	26/29	29/31		8.0 %	0.96 [0.82, 1.12]
Subtotal (95% CI)	**29**	**31**		**8.0 %**	**0.96 [0.82, 1.12]**
Total events: 26 (Restrictive), 29 (Liberal)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.54 (P = 0.59)					
6 Critical care					
Hebert 1995	18/33	35/36		6.4 %	0.56 [0.41, 0.77]
Hebert 1999	280/418	420/420		8.5 %	0.67 [0.63, 0.72]
Lacroix 2007	146/320	310/317		8.2 %	0.47 [0.41, 0.53]
Subtotal (95% CI)	**771**	**773**		**23.1 %**	**0.56 [0.42, 0.75]**
Total events: 444 (Restrictive), 765 (Liberal)					
Heterogeneity: Tau^2 = 0.06; Chi^2 = 29.71, df = 2 (P<0.00001); I^2 =93%					
Test for overall effect: Z = 3.82 (P = 0.00013)					
Total (95% CI)	**1801**	**1806**		**100.0 %**	**0.63 [0.54, 0.74]**
Total events: 883 (Restrictive), 1403 (Liberal)					
Heterogeneity: Tau^2 = 0.07; Chi^2 = 123.82, df = 14 (P<0.00001); I^2 =89%					
Test for overall effect: Z = 5.79 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.0, df = 5 (P = 0.0), I^2 =0.0%					

Analysis 1.5. Comparison 1 Blood transfusions, Outcome 5 Patients exposed to blood transfusion (by transfusion threshold).

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 1 Blood transfusions

Outcome: 5 Patients exposed to blood transfusion (by transfusion threshold)

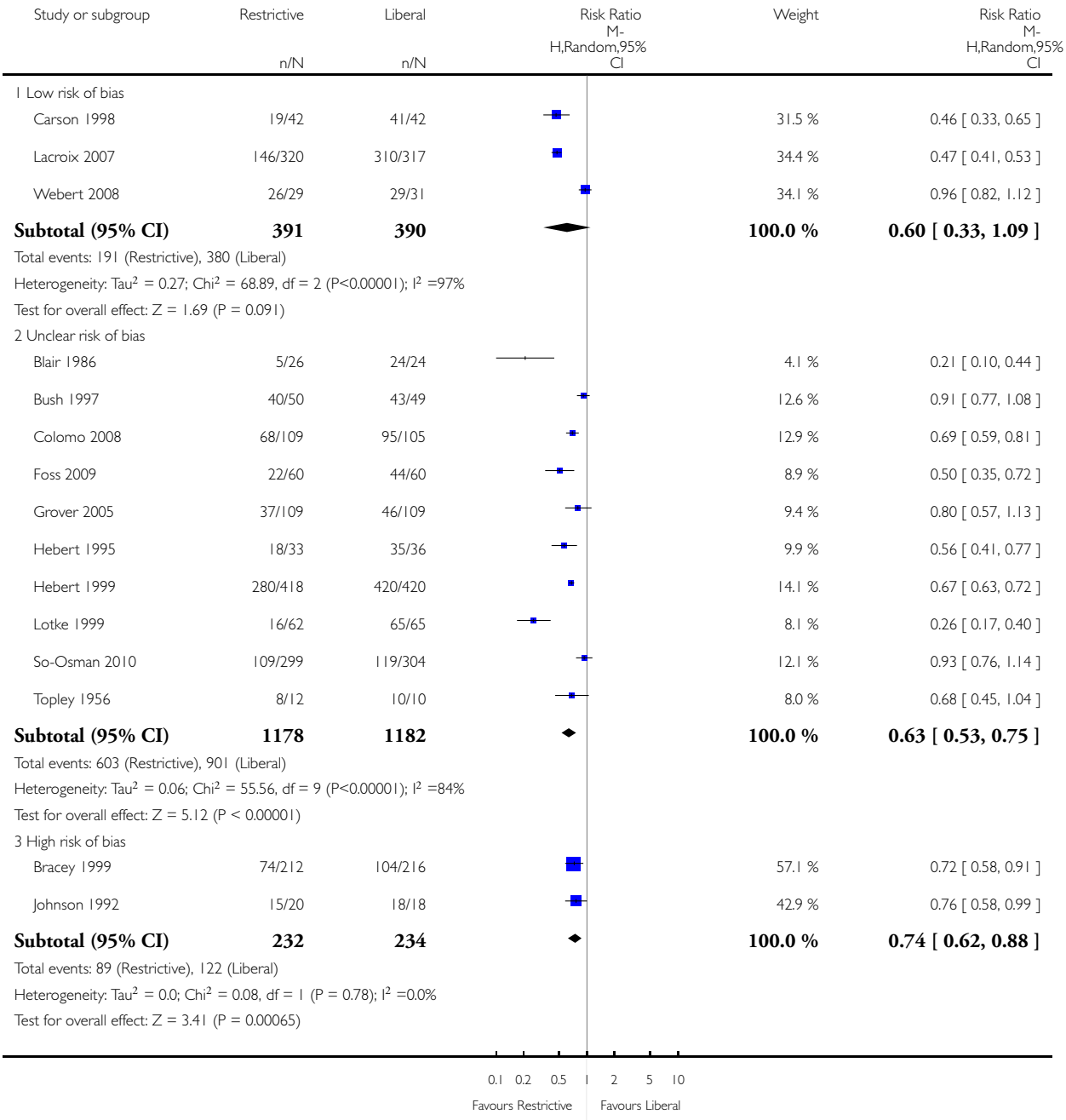


Analysis 1.6. Comparison 1 Blood transfusions, Outcome 6 Patients exposed to blood transfusion (by allocation concealment).

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 1 Blood transfusions

Outcome: 6 Patients exposed to blood transfusion (by allocation concealment)



Analysis 1.7. Comparison 1 Blood transfusions, Outcome 7 Units of blood transfused.

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 1 Blood transfusions

Outcome: 7 Units of blood transfused

Study or subgroup	Restrictive N	Mean(SD)	Liberal N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Blair 1986	26	2.6 (3)	24	4.6 (1.5)		10.2 %	-2.00 [-3.30, -0.70]
Bracey 1999	212	0.9 (1.5)	216	1.4 (1.8)		16.3 %	-0.50 [-0.81, -0.19]
Bush 1997	50	2.8 (3.1)	49	3.7 (3.5)		10.2 %	-0.90 [-2.20, 0.40]
Hebert 1999	418	2.6 (4.1)	420	5.6 (5.3)		14.6 %	-3.00 [-3.64, -2.36]
Johnson 1992	20	1 (0.86)	18	2.05 (0.93)		15.0 %	-1.05 [-1.62, -0.48]
Lacroix 2007	320	0.9 (2.6)	317	1.7 (2.2)		16.0 %	-0.80 [-1.17, -0.43]
So-Osman 2010	299	0.78 (1.4)	304	0.86 (1.6)		16.5 %	-0.08 [-0.32, 0.16]
Topley 1956	12	4.8 (6.7)	10	11.3 (6.9)		1.2 %	-6.50 [-12.21, -0.79]
Total (95% CI)	**1357**		**1358**			**100.0 %**	**-1.19 [-1.85, -0.53]**

Heterogeneity: $Tau^2 = 0.67$; $Chi^2 = 84.46$, df = 7 ($P<0.00001$); $I^2 = 92\%$

Test for overall effect: Z = 3.54 (P = 0.00040)

Analysis 1.8. Comparison 1 Blood transfusions, Outcome 8 Units of blood transfused in those transfused.

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 1 Blood transfusions

Outcome: 8 Units of blood transfused in those transfused

Study or subgroup	Restrictive N	Mean(SD)	Liberal N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Blair 1986	5	2.6 (1.34)	24	4.6 (1.47)		9.4 %	-2.00 [-3.31, -0.69]
Bracey 1999	74	2.58 (1.45)	104	2.91 (1.53)		17.7 %	-0.33 [-0.77, 0.11]
Bush 1997	40	3.5 (3.09)	43	4.22 (3.43)		8.7 %	-0.72 [-2.12, 0.68]
Carson 1998	19	1.84 (1.12)	39	2 (0.89)		16.4 %	-0.16 [-0.74, 0.42]
Hebert 1999	280	3.88 (4.49)	420	5.6 (5.3)		14.8 %	-1.72 [-2.45, -0.99]
Johnson 1992	15	1 (0.86)	18	2.05 (0.93)		16.1 %	-1.05 [-1.66, -0.44]
Lacroix 2007	146	1.9 (3.4)	310	1.7 (2.1)		16.2 %	0.20 [-0.40, 0.80]
Topley 1956	8	7.2 (7.13)	10	11.34 (6.87)		0.7 %	-4.14 [-10.66, 2.38]
Total (95% CI)	**587**		**968**			**100.0 %**	**-0.75 [-1.30, -0.20]**

Heterogeneity: $Tau^2 = 0.39$; $Chi^2 = 27.05$, df = 7 (P = 0.00033); $I^2 = 74\%$

Test for overall effect: Z = 2.69 (P = 0.0072)

Analysis 2.1. Comparison 2 Haematocrit levels, Outcome 1 Haematocrit levels - restrictive versus liberal.

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

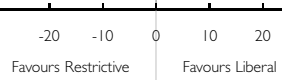
Comparison: 2 Haematocrit levels

Outcome: 1 Haematocrit levels - restrictive versus liberal

Study or subgroup	Restrictive N	Mean(SD)	Liberal N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Blair 1986	26	37 (7.1)	24	37 (7.8)		8.1 %	0.0 [-4.15, 4.15]
Bush 1997	50	29.4 (3.9)	49	33 (3.6)		11.5 %	-3.60 [-5.08, -2.12]
Carson 1998	42	29.1 (2.7)	42	32.1 (2.7)		11.8 %	-3.00 [-4.15, -1.85]
Fortune 1987	12	30.3 (2.07)	13	38.1 (2.16)		11.4 %	-7.80 [-9.46, -6.14]
Grover 2005	109	29.4 (3.69)	107	33.3 (2.79)		12.0 %	-3.90 [-4.77, -3.03]
Hebert 1999	418	25.5 (2.1)	420	32.1 (2.1)		12.3 %	-6.60 [-6.88, -6.32]
Lacroix 2007	320	28.2 (3.6)	317	33.6 (3.3)		12.2 %	-5.40 [-5.94, -4.86]
So-Osman 2010	299	34.2 (3.3)	304	34.2 (3.9)		12.2 %	0.0 [-0.58, 0.58]
Topley 1956	12	33.75 (2.15)	10	46.68 (5.97)		8.4 %	-12.93 [-16.83, -9.03]
Total (95% CI)	**1288**		**1286**			**100.0 %**	**-4.69 [-6.71, -2.67]**

Heterogeneity: $Tau^2 = 8.61$; $Chi^2 = 463.96$, df = 8 ($P<0.00001$); $I^2 = 98\%$

Test for overall effect: $Z = 4.55$ ($P < 0.00001$)



Analysis 3.1. Comparison 3 Mortality, Outcome 1 ≤14-day mortality.

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 3 Mortality

Outcome: 1 ≤14-day mortality

Study or subgroup	Restrictive n/N	Liberal n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Grover 2005	0/109	1/109		36.1 %	0.33 [0.01, 8.09]
So-Osman 2010	1/299	2/304		63.9 %	0.51 [0.05, 5.58]
Total (95% CI)	**408**	**413**		**100.0 %**	**0.44 [0.06, 2.96]**

Total events: 1 (Restrictive), 3 (Liberal)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.04$, df = 1 (P = 0.84); $I^2 = 0.0\%$

Test for overall effect: Z = 0.85 (P = 0.40)

Test for subgroup differences: Not applicable

Analysis 3.2. Comparison 3 Mortality, Outcome 2 30-day mortality.

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 3 Mortality

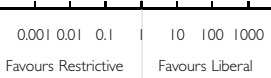
Outcome: 2 30-day mortality

Study or subgroup	Restrictive n/N	Liberal n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Blair 1986	0/26	2/24		0.6 %	0.19 [0.01, 3.67]
Bracey 1999	3/215	6/222		2.8 %	0.52 [0.13, 2.04]
Bush 1997	4/50	4/49		3.0 %	0.98 [0.26, 3.70]
Carson 1998	1/42	1/42		0.7 %	1.00 [0.06, 15.47]
Foss 2009	5/60	0/60		0.6 %	11.00 [0.62, 194.63]
Hebert 1995	8/33	9/36		7.7 %	0.97 [0.42, 2.22]
Hebert 1999	78/418	98/420		74.7 %	0.80 [0.61, 1.04]
Lacroix 2007	14/320	14/317		10.0 %	0.99 [0.48, 2.04]
Lotke 1999	0/62	0/65			Not estimable
Total (95% CI)	**1226**	**1235**		**100.0 %**	**0.83 [0.66, 1.05]**

Total events: 113 (Restrictive), 134 (Liberal)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.09$, df = 7 (P = 0.65); $I^2 = 0.0\%$

Test for overall effect: Z = 1.57 (P = 0.12)

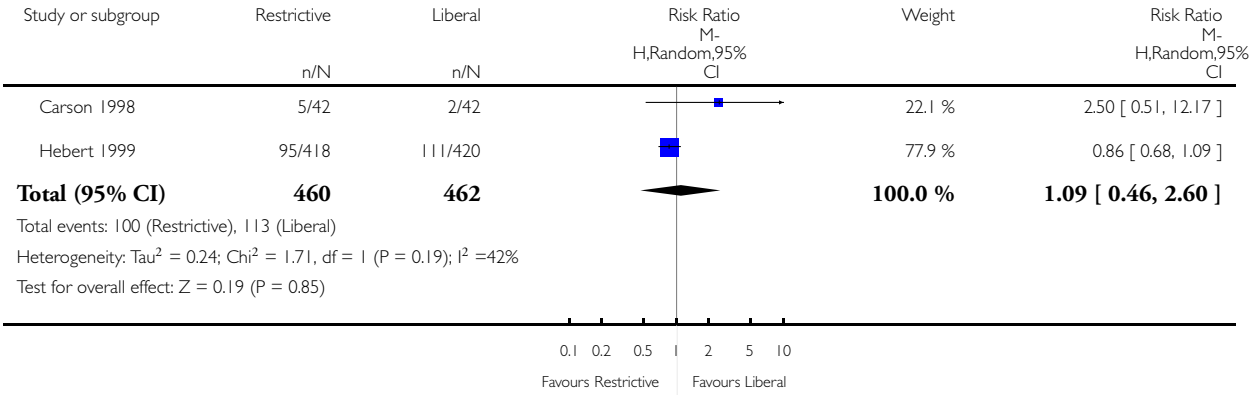


Analysis 3.3. Comparison 3 Mortality, Outcome 3 60-day mortality.

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 3 Mortality

Outcome: 3 60-day mortality

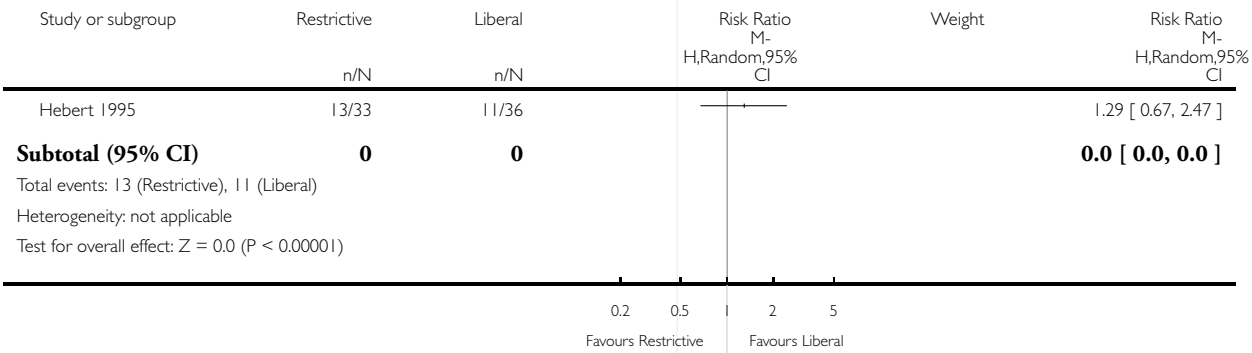


Analysis 3.4. Comparison 3 Mortality, Outcome 4 120-day mortality.

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 3 Mortality

Outcome: 4 120-day mortality



Analysis 3.5. Comparison 3 Mortality, Outcome 5 Hospital mortality.

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 3 Mortality

Outcome: 5 Hospital mortality

Study or subgroup	Restrictive n/N	Liberal n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Blair 1986	0/26	2/24		0.6 %	0.19 [0.01, 3.67]
Bracey 1999	3/215	6/222		2.8 %	0.52 [0.13, 2.04]
Carson 1998	0/42	0/42			Not estimable
Hebert 1999	93/418	118/420		96.6 %	0.79 [0.63, 1.00]
Total (95% CI)	**701**	**708**		**100.0 %**	**0.78 [0.62, 0.98]**

Total events: 96 (Restrictive), 126 (Liberal)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.26$, df = 2 (P = 0.53); $I^2 = 0.0\%$

Test for overall effect: Z = 2.15 (P = 0.031)

Analysis 3.6. Comparison 3 Mortality, Outcome 6 ICU mortality.

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 3 Mortality

Outcome: 6 ICU mortality

Study or subgroup	Restrictive n/N	Liberal n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Hebert 1995	5/33	7/36		40.1 %	0.78 [0.27, 2.22]
Lacroix 2007	11/320	8/317		54.5 %	1.36 [0.56, 3.34]
Zygun 2009	3/20	0/10		5.3 %	3.67 [0.21, 64.80]
Total (95% CI)	**373**	**363**		**100.0 %**	**1.15 [0.59, 2.23]**

Total events: 19 (Restrictive), 15 (Liberal)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.32$, df = 2 (P = 0.52); $I^2 = 0.0\%$

Test for overall effect: Z = 0.41 (P = 0.68)

Analysis 3.7. Comparison 3 Mortality, Outcome 7 Mortality (unspecified follow-up period).

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 3 Mortality

Outcome: 7 Mortality (unspecified follow-up period)

Study or subgroup	Restrictive n/N	Liberal n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Colomo 2008	12/109	17/105			0.68 [0.34, 1.35]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**

Total events: 12 (Restrictive), 17 (Liberal)

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)

Analysis 4.1. Comparison 4 Length of stay, Outcome 1 Hospital length of stay.

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 4 Length of stay

Outcome: 1 Hospital length of stay

Study or subgroup	Restrictive N	Mean(SD)	Liberal N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Bracey 1999	212	7.5 (2.9)	216	7.9 (4.9)		46.5 %	-0.40 [-1.16, 0.36]
Bush 1997	50	10 (6)	49	11 (9)		3.0 %	-1.00 [-4.02, 2.02]
Carson 1998	42	6.4 (3.4)	42	6.3 (3.4)		12.7 %	0.10 [-1.35, 1.55]
Foss 2009	60	17 (12.9)	60	18.4 (14.4)		1.1 %	-1.40 [-6.29, 3.49]
Hebert 1999	418	34.8 (19.5)	420	35.5 (19.4)		3.9 %	-0.70 [-3.33, 1.93]
Johnson 1992	20	7.9 (4.3)	18	7.6 (1.9)		6.2 %	0.30 [-1.78, 2.38]
So-Osman 2010	299	9.6 (5)	304	10.2 (7.4)		26.6 %	-0.60 [-1.61, 0.41]
Total (95% CI)	**1101**		**1109**			**100.0 %**	**-0.39 [-0.91, 0.13]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.40$, df = 6 (P = 0.97); $I^2 = 0.0\%$

Test for overall effect: Z = 1.46 (P = 0.14)

Analysis 4.2. Comparison 4 Length of stay, Outcome 2 ICU length of stay.

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 4 Length of stay

Outcome: 2 ICU length of stay

Study or subgroup	Restrictive N	Mean(SD)	Liberal N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Bush 1997	50	4 (4)	49	4 (8)		9.4 %	0.0 [-2.50, 2.50]
Hebert 1999	418	11 (10.7)	420	11.5 (11.3)		26.4 %	-0.50 [-1.99, 0.99]
Johnson 1992	20	3.2 (0.7)	18	3.3 (3.4)		22.8 %	-0.10 [-1.70, 1.50]
Lacroix 2007	320	9.5 (7.9)	317	9.9 (7.4)		41.4 %	-0.40 [-1.59, 0.79]
Total (95% CI)	**808**		**804**			**100.0 %**	**-0.32 [-1.09, 0.44]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.21$, df = 3 (P = 0.98); $I^2 = 0.0\%$

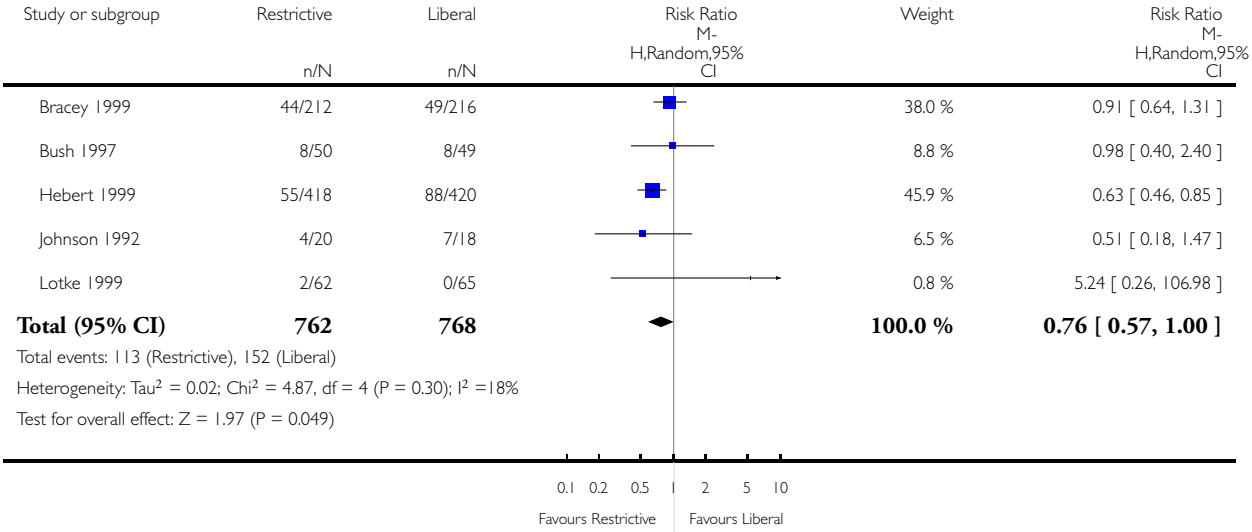
Test for overall effect: Z = 0.82 (P = 0.41)

Analysis 5.1. Comparison 5 Adverse events, Outcome 1 Cardiac events.

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 5 Adverse events

Outcome: 1 Cardiac events

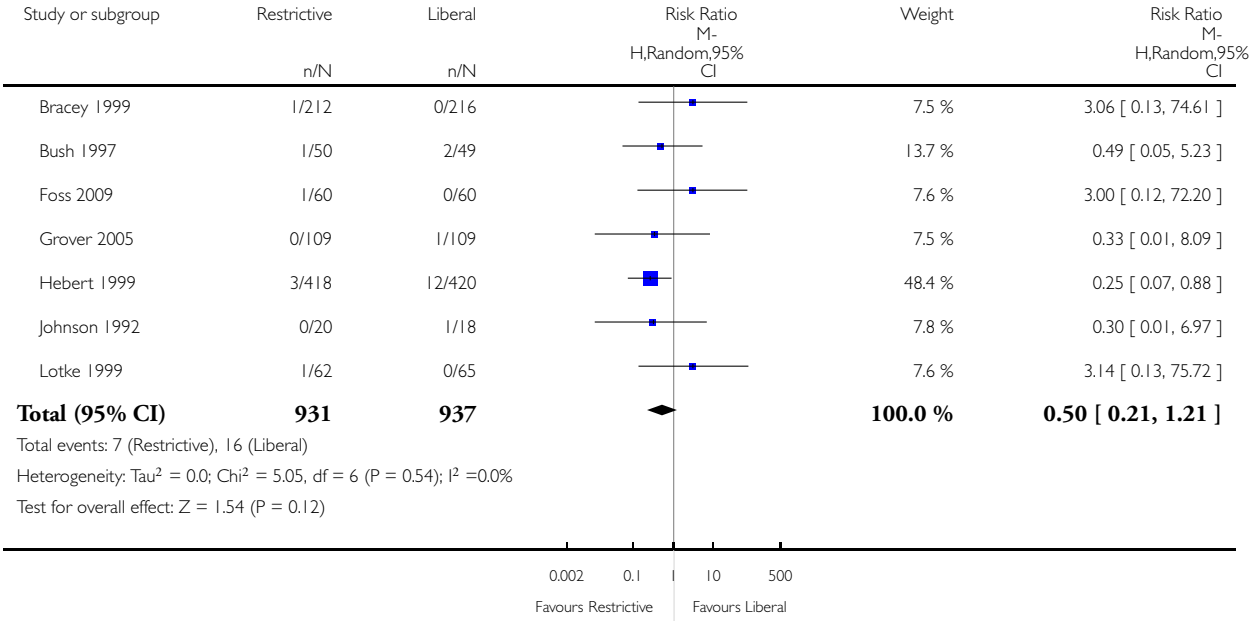


Analysis 5.2. Comparison 5 Adverse events, Outcome 2 Myocardial infarction.

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 5 Adverse events

Outcome: 2 Myocardial infarction



Analysis 5.3. Comparison 5 Adverse events, Outcome 3 Pulmonary oedema.

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 5 Adverse events

Outcome: 3 Pulmonary oedema

Study or subgroup	Restrictive n/N	Liberal n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Foss 2009	2/60	0/60		9.4 %	5.00 [0.25, 102.00]
Hebert 1999	22/418	45/420		71.6 %	0.49 [0.30, 0.80]
Johnson 1992	0/20	1/18		8.8 %	0.30 [0.01, 6.97]
Lacroix 2007	0/320	5/317		10.2 %	0.09 [0.01, 1.62]
Total (95% CI)	**818**	**815**		**100.0 %**	**0.49 [0.18, 1.31]**

Total events: 24 (Restrictive), 51 (Liberal)

Heterogeneity: $Tau^2 = 0.29$; $Chi^2 = 3.69$, df = 3 (P = 0.30); $I^2 = 19\%$

Test for overall effect: Z = 1.41 (P = 0.16)

Analysis 5.4. Comparison 5 Adverse events, Outcome 4 Cerebrovascular accident (CVA) - stroke.

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 5 Adverse events

Outcome: 4 Cerebrovascular accident (CVA) - stroke

Study or subgroup	Restrictive n/N	Liberal n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Carson 1998	0/42	1/42		29.8 %	0.33 [0.01, 7.96]
Foss 2009	1/60	1/60		39.7 %	1.00 [0.06, 15.62]
Johnson 1992	1/20	0/18		30.4 %	2.71 [0.12, 62.70]
Total (95% CI)	**122**	**120**		**100.0 %**	**0.98 [0.17, 5.52]**

Total events: 2 (Restrictive), 2 (Liberal)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.85$, df = 2 (P = 0.65); $I^2 = 0.0\%$

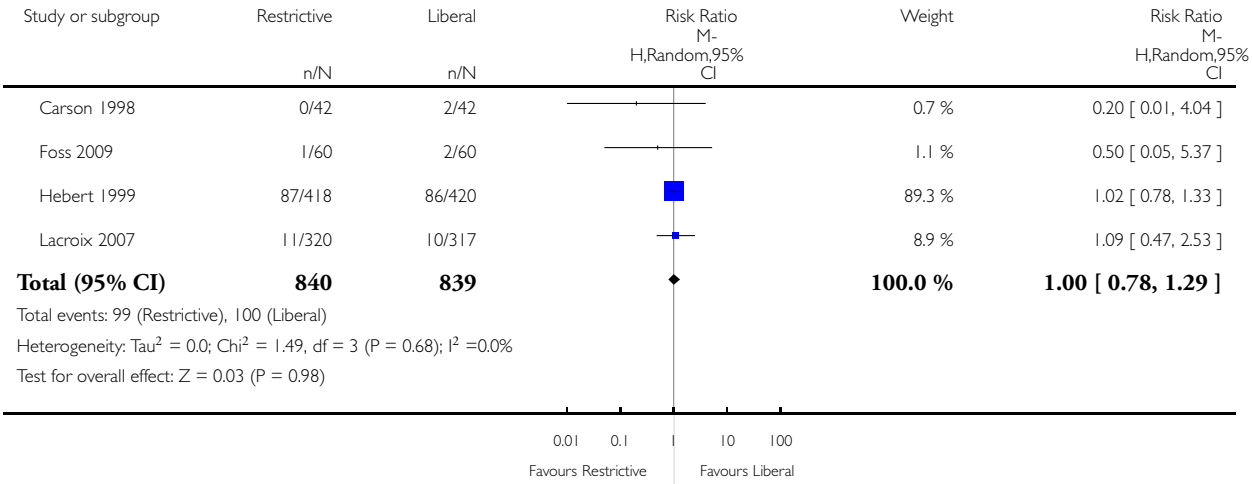
Test for overall effect: Z = 0.03 (P = 0.98)

Analysis 5.5. Comparison 5 Adverse events, Outcome 5 Pneumonia.

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 5 Adverse events

Outcome: 5 Pneumonia

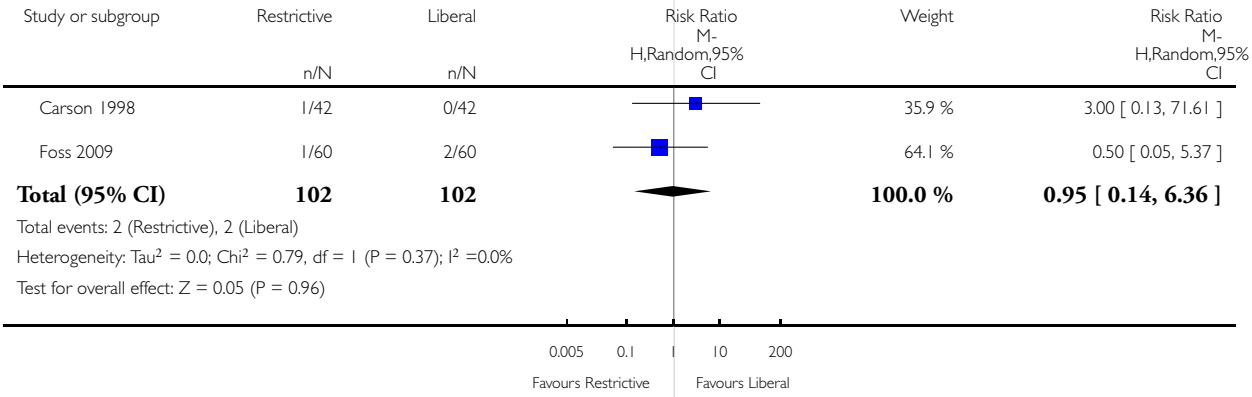


Analysis 5.6. Comparison 5 Adverse events, Outcome 6 Thromboembolism.

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 5 Adverse events

Outcome: 6 Thromboembolism



Analysis 5.7. Comparison 5 Adverse events, Outcome 7 Rebleeding.

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 5 Adverse events

Outcome: 7 Rebleeding

Study or subgroup	Restrictive n/N	Liberal n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Blair 1986	1/26	9/24			0.10 [0.01, 0.75]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**
Total events: 1 (Restrictive), 9 (Liberal)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					

Analysis 5.8. Comparison 5 Adverse events, Outcome 8 Infection.

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 5 Adverse events

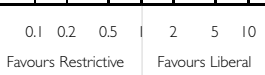
Outcome: 8 Infection

Study or subgroup	Restrictive n/N	Liberal n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Bracey 1999	5/212	3/216		3.0 %	1.70 [0.41, 7.02]
Foss 2009	6/60	11/60		6.9 %	0.55 [0.22, 1.38]
Lacroix 2007	65/320	79/317		71.1 %	0.82 [0.61, 1.09]
So-Osman 2010	18/299	31/304		19.1 %	0.59 [0.34, 1.03]
Total (95% CI)	**891**	**897**		**100.0 %**	**0.76 [0.60, 0.97]**

Total events: 94 (Restrictive), 124 (Liberal)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.74$, df = 3 (P = 0.43); $I^2 = 0.0\%$

Test for overall effect: Z = 2.19 (P = 0.029)



Analysis 5.9. Comparison 5 Adverse events, Outcome 9 Renal failure.

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 5 Adverse events

Outcome: 9 Renal failure

Study or subgroup	Restrictive n/N	Liberal n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Bracey 1999	8/212	5/216		88.3 %	1.63 [0.54, 4.90]
Lacroix 2007	2/320	0/317		11.7 %	4.95 [0.24, 102.77]
Total (95% CI)	**532**	**533**		**100.0 %**	**1.86 [0.66, 5.22]**

Total events: 10 (Restrictive), 5 (Liberal)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.46$, df = 1 (P = 0.50); $I^2 = 0.0\%$

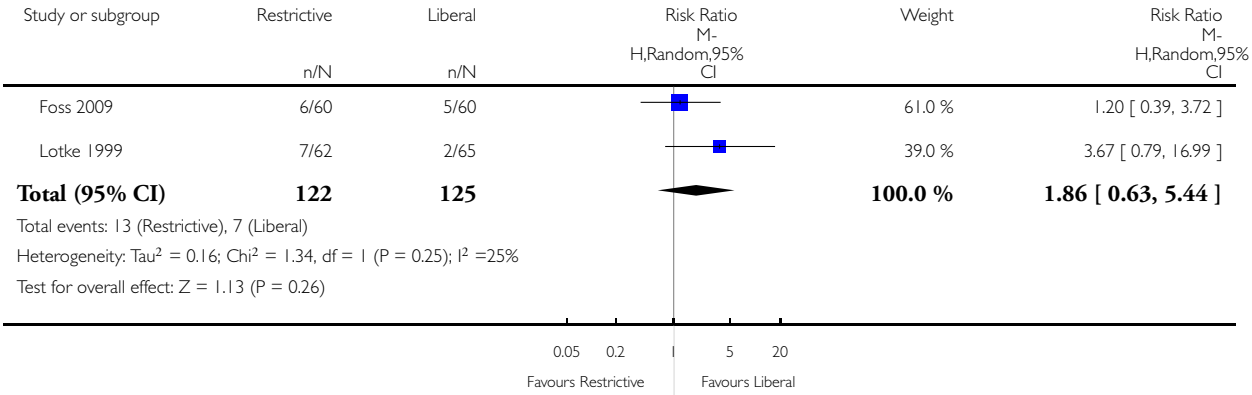
Test for overall effect: Z = 1.17 (P = 0.24)

Analysis 5.10. Comparison 5 Adverse events, Outcome 10 Mental confusion.

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Comparison: 5 Adverse events

Outcome: 10 Mental confusion



APPENDICES

Appendix 1. Search strategy

CENTRAL (*the Cochrane Library 2009, Issue 3): 138 records*

#1 MeSH descriptor Blood Transfusion, this term only with qualifiers: MT,ST

#2 transfus* near5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard*)

#3 (Red blood cell* or RBC) near5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard*) and (therap* or transfus*)

#4 (H?emoglobin or h?emocrit or HB or HCT) near5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard*)

#5 transfus* near5 (restrict* or liberal*)

#6 (blood transfus*) near3 (management or program*)

#7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6) (from 2004 to 2009)

Ovid MEDLINE(R) 1950 to August Week 2 2009: 505 records

1. *Blood Transfusion/
2. ((Red blood cell* or RBC) adj3 (therap* or transfus*)).mp.

3. 1 or 2
4. exp Reference Standards/
5. standards.fs.
6. methods.fs.
7. 4 or 5 or 6
8. 3 and 7
9. (transfus* adj5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard*)).mp.
10. ((Red blood cell* or RBC) adj5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard*)).mp.
11. ((H?emoglobin or h?emocrit or HB or HCT) adj5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard*)).mp.
12. (transfus* adj5 (restrict* or liberal*)).mp.
13. ((blood or transfus*) adj3 (management or program*)).mp.
14. 8 or 9 or 10 or 11 or 12 or 13
15. randomi?ed.ab,ti.
16. randomized controlled trial.pt.
17. controlled clinical trial.pt.
18. placebo.ab.
19. clinical trials as topic.sh.
20. randomly.ab.
21. trial.ti.
22. 15 or 16 or 17 or 18 or 19 or 20 or 21
23. (animals not (humans and animals)).sh.
24. 22 not 23
25. 24 and 14
26. (2004* or 2005* or 2006* or 2007* or 2008* or 2009*).em.
27. 26 and 25

EMBASE 1980 to 2009 Week 33: 572 records

1. *Blood Transfusion/
2. ((Red blood cell* or RBC) adj3 (therap* or transfus*)).mp.
3. (transfus* adj5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard*)).mp.
4. ((Red blood cell* or RBC) adj5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard*)).mp.
5. ((H?emoglobin or h?emocrit or HB or HCT) adj5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard*)).mp.
6. (transfus* adj5 (restrict* or liberal*)).mp.
7. ((blood or transfus*) adj3 (management or program*)).mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp Randomized Controlled Trial/
10. exp controlled clinical trial/
11. randomi?ed.ab,ti.
12. placebo.ab.
13. *Clinical Trial/
14. randomly.ab.
15. trial.ti.
16. 9 or 10 or 11 or 12 or 13 or 14 or 15
17. exp animal/ not (exp human/ and exp animal/)
18. 16 not 17
19. 8 and 18
20. (2004* or 2005* or 2006* or 2007* or 2008* or 2009*).em.
21. 19 and 20

ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) 2004 to August 2009

ISI Web of Science: Conference Proceedings Citation Index- Science (CPCI-S) 2004 to August 2009: 214 records

#1 Topic=(Blood or "Red blood cell" or "Red blood cells" or RBC or Hemoglobin* or haemoglobin* or haemocrit or hemocrit or HB or HCT) AND Topic=(transfus*) AND Topic=(polic* or practice or protocol* or trigger* or threshold* or indicator* or strateg* or criteri* or standard* or restrict* or liberal* or management or program*)
#2 Topic=(randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial) OR Topic=(controlled clinical trial OR controlled trial OR clinical trial OR placebo)
#3 Topic=((singl* OR doubl* OR trebl* OR tripl*) SAME (blind* OR mask*))
#4 #2 or #3
#5 Topic=(human*)
#6 #4 and #5
#7 #1 and #6

WHAT'S NEW

Last assessed as up-to-date: 31 July 2009.

Date	Event	Description
12 February 2010	New citation required but conclusions have not changed	The searches were updated to August 2009, seven new trials have been included and the Results amended accordingly. The Background section of the review has been updated. The overall conclusions of the review remain unchanged As part of this update the assessment of methodological quality used in earlier versions of this review has been replaced with an assessment of the risk of bias. This amendment is in accordance to a change in the Cochrane Collaboration's methodological guidance

HISTORY

Protocol first published: Issue 2, 2000

Review first published: Issue 2, 2002

Date	Event	Description
9 September 2008	Amended	Converted to new review format.
17 November 2004	New search has been performed	An updated search for new trials was conducted in November 2004. No new trials for inclusion were identified

CONTRIBUTIONS OF AUTHORS

Contributors (names are listed alphabetically):

Paul Carless (University of Newcastle) performed computer database literature searches, screened abstracts and titles for relevant articles, obtained relevant papers, applied inclusion/exclusion criteria to retrieved papers, extracted data from the trials, quality assessed trials, entered data into Meta-View 4.1, entered all study details into Review Manager 4.1, and co-wrote the review; Jeffrey Carson (Robert Wood Johnson Medical School) provided expert opinion, co-wrote review; Paul Hebert (Ottawa General Hosptial) provided expert opinion; David Henry (Institute of Clinical Evaluative Sciences) co-wrote review; Katharine Ker (London School of Hygiene & Tropical Medicine) undertook the following tasks for the 2010 update - screened search output, obtained articles, applied inclusion/exclusion criteria to retrieved papers, assessed risk of bias, extracted data, performed data analysis and revised the text of the review; Brian McClelland (Scottish National Blood Transfusion Service) provided expert opinion.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NSW Ministerial Advisory Committee on Quality in Health Care, Australia.
- NSW Health Department, Australia.

INDEX TERMS

Medical Subject Headings (MeSH)

Erythrocyte Transfusion [adverse effects; mortality; *standards]; Guidelines as Topic; Hemoglobin A [analysis]; Randomized Controlled Trials as Topic; Reference Values; Transplantation, Autologous; Transplantation, Homologous

MeSH check words

Humans