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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	3
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	5
BACKGROUND	7
OBJECTIVES	8
METHODS	8
RESULTS	12
Figure 1.	13
Figure 2.	16
Figure 3.	17
ADDITIONAL SUMMARY OF FINDINGS	23
DISCUSSION	27
AUTHORS' CONCLUSIONS	29
ACKNOWLEDGEMENTS	30
REFERENCES	30
CHARACTERISTICS OF STUDIES	33
DATA AND ANALYSES	43
Analysis 1.1. Comparison 1 Aggressive versus conservative blood transfusion, Outcome 1 Serious complications related to sickle cell disease.	45
Analysis 1.2. Comparison 1 Aggressive versus conservative blood transfusion, Outcome 2 Serious infection.	46
Analysis 1.3. Comparison 1 Aggressive versus conservative blood transfusion, Outcome 3 Perioperative complications.	46
Analysis 1.4. Comparison 1 Aggressive versus conservative blood transfusion, Outcome 4 Postoperative complications.	47
Analysis 1.5. Comparison 1 Aggressive versus conservative blood transfusion, Outcome 5 Transfusion-related complications.	48
Analysis 1.6. Comparison 1 Aggressive versus conservative blood transfusion, Outcome 6 Cholecystectomy preoperative haemoglobin.	48
Analysis 1.7. Comparison 1 Aggressive versus conservative blood transfusion, Outcome 7 Cholecystectomy preoperative haemoglobin S.	49
Analysis 1.8. Comparison 1 Aggressive versus conservative blood transfusion, Outcome 8 Cholecystectomy volume of blood transfusion/venesection.	50
Analysis 2.1. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 1 Serious complications related to sickle cell disease (acute chest syndrome).	50
Analysis 2.2. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 2 Serious complications related to sickle cell disease.	51
Analysis 2.3. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 3 Serious infection.	52
Analysis 2.4. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 4 Perioperative complications.	52
Analysis 2.5. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 5 Perioperative complications (respiratory).	53
Analysis 2.6. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 6 Postoperative complications (wound complications).	54
Analysis 2.7. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 7 Transfusion-related complications (serious).	54
Analysis 2.8. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 8 Transfusion-related complications (new alloantibody).	55
Analysis 2.9. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 9 Transfusion-related complications (transfusion reactions).	55
Analysis 2.10. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 10 Length of stay.	56
Analysis 2.11. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 11 Quality of life.	56
Analysis 2.12. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 12 Haemoglobin concentration.	57

Analysis 2.13. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 13 Haemoglobin S.	57
Analysis 2.14. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 14 Number of units or volume of red cells transfused.	58
APPENDICES	58
WHAT'S NEW	60
HISTORY	61
CONTRIBUTIONS OF AUTHORS	62
DECLARATIONS OF INTEREST	62
SOURCES OF SUPPORT	63
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	63
INDEX TERMS	64

Preoperative blood transfusions for sickle cell disease

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ABSTRACT

Background

Sickle cell disease is one of the commonest severe monogenic disorders in the world, due to the inheritance of two abnormal haemoglobin (beta globin) genes. Sickle cell disease can cause severe pain, significant end-organ damage, pulmonary complications, and premature death. Surgical interventions are more common in people with sickle cell disease, and occur at much younger ages than in the general population. Blood transfusions are frequently used prior to surgery and several regimens are used but there is no consensus over the best method or the necessity of transfusion in specific surgical cases. This is an update of a Cochrane review first published in 2001.

Objectives

To determine whether there is evidence that preoperative blood transfusion in people with sickle cell disease undergoing elective or emergency surgery reduces mortality and perioperative or sickle cell-related serious adverse events.

To compare the effectiveness of different transfusion regimens (aggressive or conservative) if preoperative transfusions are indicated in people with sickle cell disease.

Search methods

We searched for relevant trials in *The Cochrane Library*, MEDLINE (from 1946), Embase (from 1974), the Transfusion Evidence Library (from 1980), and ongoing trial databases; all searches current to 23 March 2016.

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register: 18 January 2016.

Selection criteria

All randomised controlled trials and quasi-randomised controlled trials comparing preoperative blood transfusion regimens to different regimens or no transfusion in people with sickle cell disease undergoing elective or emergency surgery. There was no restriction by outcomes examined, language or publication status.

Data collection and analysis

Two authors independently assessed trial eligibility and the risk of bias and extracted data.

Main results

Three trials with 990 participants were eligible for inclusion in the review. There were no ongoing trials identified. These trials were conducted between 1988 and 2011. The majority of people included had haemoglobin (Hb) SS SCD. The majority of surgical procedures were considered low or intermediate risk for developing sickle cell-related complications.

Aggressive versus simple red blood cell transfusions

One trial (551 participants) compared an aggressive transfusion regimen (decreasing sickle haemoglobin to less than 30%) to a simple transfusion regimen (increasing haemoglobin to 100 g/l). This trial re-randomised participants and therefore quantitative analysis was only possible on two subsets of data: participants undergoing cholecystectomy (230 participants); and participants undergoing tonsillectomy or adenoidectomy surgeries (107 participants). Data were not combined as we do not know if any participant received both surgeries. Overall, the quality of the evidence was very low across different outcomes according to GRADE methodology. This was due to the trial being at high risk of bias primarily due to lack of blinding, indirectness and the outcome estimates being imprecise. Cholecystectomy subgroup results are reported in the abstract. Results for both subgroups were similar.

There was no difference in all-cause mortality between people receiving aggressive transfusions and those receiving conservative transfusions. No deaths occurred in either subgroup.

There were no differences between the aggressive transfusion group and conservative transfusion group in the number of people developing:

- an acute chest syndrome, risk ratio 0.84 (95% confidence interval 0.38 to 1.84) (one trial, 230 participants, very low quality evidence);
- vaso-occlusive crisis, risk ratio 0.30 (95% confidence interval 0.09 to 1.04) (one trial, 230 participants, very low quality evidence);
- serious infection, risk ratio 1.75 (95% confidence interval 0.59 to 5.18) (one trial, 230 participants, very low quality evidence);
- any perioperative complications, risk ratio 0.75 (95% confidence interval 0.36 to 1.55) (one trial, 230 participants, very low quality evidence);
- a transfusion-related complication, risk ratio 1.85 (95% confidence interval 0.89 to 3.88) (one trial, 230 participants, very low quality evidence).

Preoperative transfusion versus no preoperative transfusion

Two trials (434 participants) compared a preoperative transfusion plus standard care to a group receiving standard care. Overall, the quality of the evidence was low to very low across different outcomes according to GRADE methodology. This was due to the trials being at high risk of bias due to lack of blinding, and outcome estimates being imprecise. One trial was stopped early because more people in the no transfusion arm developed an acute chest syndrome.

There was no difference in all-cause mortality between people receiving preoperative transfusions and those receiving no preoperative transfusions (two trials, 434 participants, no deaths occurred).

There was significant heterogeneity between the two trials in the number of people developing an acute chest syndrome, a meta-analysis was therefore not performed. One trial showed a reduced number of people developing acute chest syndrome between people receiving preoperative transfusions and those receiving no preoperative transfusions, risk ratio 0.11 (95% confidence interval 0.01 to 0.80) (65 participants), whereas the other trial did not, risk ratio 4.81 (95% confidence interval 0.23 to 99.61) (369 participants).

There were no differences between the preoperative transfusion groups and the groups without preoperative transfusion in the number of people developing:

- a vaso-occlusive crisis, Peto odds ratio 1.91 (95% confidence interval 0.61 to 6.04) (two trials, 434 participants, very low quality evidence).
- a serious infection, Peto odds ratio 1.29 (95% confidence interval 0.29 to 5.71) (two trials, 434 participants, very low quality evidence);
- any perioperative complications, risk ratio 0.24 (95% confidence interval 0.03 to 2.05) (one trial, 65 participants, low quality evidence).

There was an increase in the number of people developing circulatory overload in those receiving preoperative transfusions compared to those not receiving preoperative transfusions in one of the two trials, and no events were seen in the other trial (no meta-analysis performed).

Authors' conclusions

There is insufficient evidence from randomised trials to determine whether conservative preoperative blood transfusion is as effective as aggressive preoperative blood transfusion in preventing sickle-related or surgery-related complications in people with HbSS disease. There is very low quality evidence that preoperative blood transfusion may prevent development of acute chest syndrome.

Due to lack of evidence this review cannot comment on management for people with HbSC or HbS β^+ disease or for those with high baseline haemoglobin concentrations.

PLAIN LANGUAGE SUMMARY

Blood transfusions for people with sickle cell disease before they undergo surgery

Review question

We wanted to determine if blood transfusions given to people with sickle cell disease before routine or emergency surgery prevent complications due to sickle cell disease or surgery without causing any severe side effects. We also wanted to determine if any particular type of transfusion regimen is better in people with sickle cell disease undergoing surgery.

Background

Sickle cell disease is a serious inherited blood disorder where the red blood cells, which carry oxygen around the body, develop abnormally. The disorder mainly affects people of African, Caribbean, Middle Eastern, Eastern Mediterranean and Asian origin.

Normal red blood cells are flexible and disc-shaped, but in sickle cell disease they can become rigid and crescent shaped. Sickled cells are not only less flexible than healthy red blood cells, they are also stickier. This can lead to blockage of blood vessels, resulting in tissue and organ damage and episodes of severe pain. The abnormal blood cells are more fragile and break apart, which leads to a shortage of red blood cells, known as anaemia.

People with sickle cell disease are more likely to require surgery than the general population because of complications due to sickle cell disease, such as gallstones, infections, and joint problems. However, surgery can lead to sickle cell-related complications.

Blood transfusions before an operation may help prevent complications by reducing the level of anaemia, diluting the sickled red blood cells, and increasing the level of oxygen in the blood. This may reduce the risk of blood vessels becoming blocked causing further damage.

There are different types of blood transfusions. The main aim of an aggressive transfusion regimen is to reduce the number of sickled cells in the blood to below a certain level (usually sickled cells are removed and donor red cells given (exchange transfusion)), it also reduces the level of anaemia. The main aim of a conservative transfusion regimen is to reduce the level of anaemia, it also reduces the percentage of sickled cells in the blood (dilution effect) but no sickled cells are removed. An aggressive transfusion regimen decreases the percentage of sickled cells in the blood to a much lower level than a conservative transfusion regimen.

Blood transfusions can be linked to adverse events such as: the development of antibodies to proteins on donor red cells (alloimmunisation); accumulation of too much iron in the body from repeated transfusions; increased infection rates after surgery; and extended length of stay in hospital. Some types of surgery may not require blood transfusion.

Study characteristics

We searched the medical literature to 23 March 2016. We included three trials with 990 people in this review. One trial compared aggressive transfusion to conservative transfusion. Two trials compared aggressive or conservative transfusion before surgery to no transfusion. The majority of people within the trials had one form of sickle cell disease (HbSS). The majority of the operations were those considered to be at low or intermediate risk for causing sickle cell-related complications.

Two of the three trials received government funding, the third trial did not report the funding source.

Key results

There was no difference between giving a blood transfusion before surgery to reduce the number of sickled cells below a certain low level (aggressive transfusion regimen) and giving a blood transfusion to increase the number of red cells in the blood (conservative transfusion regimen) in preventing surgical or sickle-related complications immediately after surgery.

Giving a blood transfusion before surgery may prevent development of sickle-related lung problems. One trial was stopped early because more people developed sickle-related lung problems in the no transfusion arm; however, the other trial did not show a difference. There was no difference between giving a blood transfusion before surgery compared to not giving a blood transfusion before surgery in preventing any other sickle-related or surgical complications immediately after surgery.

Quality of the evidence

The quality of evidence was rated as very low for this review's outcomes due to trials being at high risk of bias and because there was a small number of trials and a small number of participants included in the trials.

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

Aggressive versus conservative blood transfusion for SCD						
Patient or population: people with SCD Settings: hospital inpatients Intervention: aggressive versus conservative blood transfusion						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Conservative transfusion	blood Aggressive blood transfusion				
Mortality Follow up: 0 - 30 days	See comment	See comment	Not estimable	230 (1 trial)	See comment	There were no deaths reported
Serious complications related to SCD - cholecystectomy ACS Follow up: 0 - 30 days	108 per 1000	91 per 1000 (41 to 199)	RR 0.84 (0.38 to 1.84)	230 (1 trial)	⊕○○○ very low ^{1,2}	
Serious complications related to SCD - cholecystectomy painful crisis Follow up: 0 - 30 days	92 per 1000	28 per 1000 (8 to 95)	RR 0.30 (0.09 to 1.04)	230 (1 trial)	⊕○○○ very low ^{1,2}	
Serious infection - cholecystectomy Follow up: 0 - 30 days	42 per 1000	73 per 1000 (25 to 216)	RR 1.75 (0.59 to 5.18)	230 (1 trial)	⊕○○○ very low ^{1,2}	
Perioperative complications - cholecystectomy complications (any) Follow up: 0 - 30 days	133 per 1000	100 per 1000 (48 to 207)	RR 0.75 (0.36 to 1.55)	230 (1 trial)	⊕○○○ very low ^{1,2}	

Trans-fusion-related complications - cholecystectomy complications (any) Follow up: 0 - 30 days	83 per 1000	154 per 1000 (74 to 323)	RR 1.85 (0.89 to 3.88)	230 (1 trial)	⊕○○○ very low ^{1,2}
Quality of life	Outcome not reported	Outcome not reported	Not estimable	NA	NA

*The basis for the **assumed risk** is the event rate in the control group. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ACS: acute chest syndrome; **CI:** confidence interval; **NA:** not applicable **RR:** risk ratio; **SCD:** sickle cell disease

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

¹ We downgraded the quality of evidence by 1 for high risk of performance bias and other bias, due to lack of blinding.

² We downgraded the quality of evidence by 2 for imprecision due to wide CIs of the estimates, and indirectness as results are reported for cholecystectomy subgroup only.

BACKGROUND

Description of the condition

Sickle cell disease (SCD) is a genetic haemoglobin disorder, which can cause severe pain, significant end-organ damage, pulmonary complications, and premature death (Chakravorty 2015). It is one of the most common severe monogenic disorders in the world, due to the inheritance of two abnormal haemoglobin (beta globin) genes (Rees 2010). Populations originating from sub-Saharan Africa, South America, the Caribbean, Central America, the Middle East, India and parts of the Mediterranean are predominantly affected. Reductions in infant and child mortality and increasing migration from highly affected countries have made this a worldwide problem (Piel 2012). Over 12,500 people in the UK and 100,000 in the USA suffer from the disease (NICE 2010; Pleasants 2014). A recent study estimated that approximately 305,800 babies were born with SCD in 2010, of which two thirds were born in Africa, and this could increase by 25% to approximately 404,200 by 2050 (Piel 2012).

The term 'sickle cell disease' refers to all genotypes that cause the clinical syndrome. There are three main types of SCD. Sickle cell anaemia is the most common form of the disease (up to 70% of cases of SCD in people of African origin) and is due to the inheritance of two beta globin S (β S) alleles (haemoglobin (Hb)SS). The second most common genotype (up to 30% of cases in people of African origin) is haemoglobin SC disease (HbSC disease) it is due to the co-inheritance of the β S and β C alleles and tends to be a more moderate form of the disease. The third major type of SCD occurs when β S is inherited with a β -thalassaemia allele, causing HbS/ β -thalassaemia (Rees 2010). People who have inherited a thalassaemia null mutation (HbS β^0) have a disease that is clinically indistinguishable from sickle cell anaemia, whereas people with HbS β^+ thalassaemia have a milder disorder. In developed nations, people with SCD are expected to live into their 40s, 50s and beyond, whereas in low-income countries including some African nations it is estimated that between 50% to 90% of children born with HbSS die before their fifth birthday (Gravitz 2014; Grosse 2011).

In SCD under conditions of low oxygen levels, acidity and cellular dehydration, the HbS molecules polymerise and begin to distort the red blood cells taking on the appearance of sickle-shaped cells. The main determinant of disease severity is the rate and extent of this HbS polymerisation (Rees 2010). This is exemplified by co-inheritance of genetic factors that affect the intracellular HbS or foetal haemoglobin concentration, for example the protective effects of co-inherited α -thalassaemia (Rumaney 2014; Steinberg 2012) or hereditary persistence of foetal haemoglobin (Akinsheye 2011; Steinberg 2012). Sickling of red blood cells results in two main events: blockage of blood flow resulting in organ and tissue ischaemia; and haemolytic anaemia (Sparkenbaugh 2013). Both of these processes are thought to lead to increased inflammation

and an increased tendency to develop a clot (Frenette 2007; Rees 2010). Blockage of blood flow is mediated via a dynamic interaction between sticky HbS containing red cells, the vessel wall, and white cells (Rees 2010). Sickle red blood cells also have a shorter lifespan of 10 to 12 days versus 120 days for normal red blood cells due to intravascular and extravascular haemolysis, leading to anaemia (Kato 2006a; Stanley 2013). Chronic intravascular haemolysis is associated with decreased levels of nitric oxide within the blood, development of pulmonary hypertension and ischaemic strokes (Kato 2006a; Kato 2006b).

Blood transfusions are a mainstay of treatment in SCD and 90% of adults will have received at least one red blood cell transfusion (Chou 2013a). Blood transfusion can be given by simple, top-up transfusions to increase the number of normal red blood cells or by exchange transfusion in which the HbS is replaced by healthy red blood cells with a goal of reducing HbS to below 30% (Kanter 2013). The benefits of transfusion therapy must be balanced against risks including infections, iron overload, alloimmunisation, acute or delayed haemolytic transfusion reactions, and increased complexity of compatibility testing (Chou 2013a; Chou 2013b; Porter 2013; Scheunemann 2010; Ubesie 2012).

Surgical interventions are more common in people with SCD, and occur at much younger ages than in the general population (Adam 2008). In one study the most frequently identified procedures in children include cholecystectomy, followed by tonsillectomy or adenoidectomy, splenectomy, umbilical hernia repair and appendectomy (Hyder 2013). A study in adult surgical procedures in SCD also found cholecystectomy to be the most common procedure followed by splenectomy, hip replacement and obstetric-gynaecological procedures (Adam 2008). A study from the UK in all populations found that ear, nose and throat procedures were the most common, followed by obstetric and gynaecological procedures, hip replacement and cholecystectomy (Buck 2005). In this survey, postoperative complications occurred in 20% of participants. Another study on hip arthroplasty reported a postoperative complication rate of 50% including anaemia due to haemolysis and excessive blood loss (35.7%) as well as infection and vaso-occlusive crisis (21.4%) in those receiving simple transfusions. In those with full exchange transfusions the postoperative complications were seen in 80% of participants with 25% involving acute or delayed haemolytic reactions (Ould Amar 2013).

Description of the intervention

Sickled red blood cells increase blood viscosity (resistance to flow) through the intrinsic properties of the sickled cells as well as through abnormal interactions of these cells with white cells, platelets, the vessel wall, and clotting factors. Transfusion of normal donor red blood cells is used to mitigate these effects (Yawn 2014). Blood transfusions are frequently used in preparation for surgery and several regimens are used in current clinical practice. These include 'top-up' transfusion (simple), in which normal red

cells are given to decrease anaemia and the concentration of HbS without removal of the individual's blood. In people with SCD who do not have severe anaemia 'top-up' blood transfusions can cause hyperviscosity syndrome because they raise the haemoglobin, but only marginally lower the HbS percentage (Schmalzer 1987).

Exchange transfusion involves removing some of the individual's own blood and transfusing allogeneic blood, thereby lowering the concentration of HbS through dilution. This reduces the effects of a given haemoglobin level on blood viscosity. A full exchange transfusion involves a full blood volume exchange by manual or automated apheresis, this allows for rapid lowering of the HbS level to 30% or less, and decreases anaemia. A partial (limited) exchange transfusion refers to manual removal of some of the individual's own blood, this is less effective in lowering the HbS level but is more easily performed when automated exchange is not available. In order to lower the HbS below 30%, repeat partial exchange transfusions may be necessary.

Transfusions can be done either immediately or up to 14 days prior to surgery, although in preparation for elective surgery it is usually undertaken at least 24 hours before the operation to maximise the oxygen transport capacity of the transfused blood. Various practises are used, but with no consensus over the best method or the necessity of transfusion in specific surgical cases (Buck 2005).

Why it is important to do this review

People with SCD undergoing surgical procedures have an increased risk for SCD- and non-SCD-associated complications. Transfusions are commonly used to prevent complications such as stroke, vaso-occlusive crises and acute chest syndrome (Yawn 2014). As well as the direct and indirect financial cost of red blood cell transfusions, they can adversely affect the individual, causing hyperviscous blood, (precipitating vaso-occlusion), iron overload, alloimmunisation resulting in future complicated compatibility testing, acute or delayed haemolytic transfusion reactions, infections, and longer hospital stays (Yawn 2014). These costs and adverse events are particularly relevant in the developing world where resources and equipment are limited and the infection risks of transfused blood can be higher than in developed countries (Ansong 2013). There is no consensus on the standard of practice for preoperative transfusion with various practises being used. It is important to review the literature to inform and improve standard of practice in this area.

OBJECTIVES

1. To determine whether there is evidence that preoperative blood transfusion in people with SCD undergoing elective or emergency surgery:

- i) reduces mortality;
- ii) reduces complications directly related to the surgical procedure, such as local infection and bleeding;
- iii) reduces serious perioperative complications related to SCD, including pain, acute sickle chest syndrome and the postoperative frequency and severity of infections;
- iv) is associated with severe adverse events (as reported in the included trials).

2. To compare the effectiveness of different transfusion regimens (aggressive or conservative) if preoperative transfusions are indicated in people with SCD.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials (RCTs) or quasi-RCTs in which preoperative blood transfusion regimens were compared to either no transfusion or compared different transfusion regimens, in people with SCD undergoing either elective or emergency surgery. There were no limits on language or publication status.

Types of participants

People with homozygous sickle cell disease (SS), sickle beta thalassaemia ($S\beta^0$ and $S\beta^+$) and sickle haemoglobin C disease (SC) (proven by electrophoresis and sickle solubility test, with family studies or DNA tests as appropriate) of all ages and both sexes undergoing elective or emergency surgery of any type in any setting.

Types of interventions

Preoperative blood transfusion regimens compared to no transfusion or trials comparing alternative preoperative transfusion regimens (e.g. top-up versus exchange).

Types of outcome measures

Primary outcomes

1. Perioperative mortality (all cause)

2. Serious complications related to:
 - i) SCD (e.g. acute chest syndrome, painful crisis, neurological complication, renal complication)
 - ii) surgery (e.g. fall in haemoglobin level)
 - iii) infection
 - iv) transfusion (e.g. serious transfusion reactions, other serious transfusion complications)

Secondary outcomes

1. Other transfusion-related complications, including alloimmunisation, infection from blood products, and minor transfusion reactions
2. Length of stay (intensive care unit and inpatient stay)
3. Quality of life (mobility, ability to work or attend school, self-reliance or as measured on a validated scale)
4. Measures of organ damage (postoperative difference from baseline) for example creatinine (kidney function), liver function tests, lung function tests
5. Haemoglobin level and haemoglobin S percentage (pre-transfusion, post-transfusion and postoperative)
6. Number of units or volume (mL) of red cells infused and, where known for exchange transfusions, volume of blood venesected, with haematocrit

Search methods for identification of studies

Electronic searches

We identified relevant trials from the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register using the terms: sickle cell OR (haemoglobinopathies AND general) AND blood transfusion* AND preoperative.

The Haemoglobinopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*) and weekly searches of MEDLINE. Unpublished work is identified by searching the abstract books of five major conferences: the European Haematology Association conference; the American Society of Hematology conference; the British Society for Haematology Annual Scientific Meeting; the Caribbean Health Research Council Meetings; and the National Sickle Cell Disease Program Annual Meeting. For full details of all searching activities for the register, please see the relevant section of the [Cystic Fibrosis and Genetic Disorders Group Module](#).

Date of last search of the Group's Haemoglobinopathies Trials Register: 18 January 2016.

In addition we searched the following databases for systematic reviews and RCT. The first search was conducted on 18 March 2015 and updated on 23 March 2016:

- *The Cochrane Library* (CENTRAL, DARE, HTA, NHSEED, 23 March 2016) (<http://www.cochranelibrary.com/>);
- MEDLINE (OvidSP, 1946 to 23 March 2016);
- Embase (OvidSP, 1974 to 23 March 2016);
- PubMed (epublications (publications ahead of print) only to 23 March 2016) (<http://www.ncbi.nlm.nih.gov/pubmed>);
- Transfusion Evidence Library (1950 to 23 March 2016) (<http://www.transfusionevidencelibrary.com/>),

We also searched the following trial databases for ongoing trials on 23 March 2016:

- ClinicalTrials.gov (<https://clinicaltrials.gov/>);
- WHO International Clinical Trials Registry Platform (ICTRP) (<http://www.who.int/ictip/en/>);
- ISRCTN Registry (<http://www.isrctn.com/>).

The full search strategies for each database are available in an appendix ([Appendix 1](#)).

Searching other resources

We augmented database searching with the following:

Handsearching of reference lists

We checked references of all included trials, relevant review articles and current treatment guidelines for further literature. These searches were limited to the 'first generation' reference lists.

Personal contacts

We contacted authors of relevant studies for unpublished material or further information.

Data collection and analysis

Selection of studies

Two independent review authors (PF, LE) screened all electronically-derived citations and abstracts of papers identified by the review search strategy for relevance. We excluded trials that were clearly irrelevant at this stage based on a review of the abstract. Two independent review authors (PF, LE) formally assessed the full texts of all potentially-relevant trials for eligibility against the criteria outlined above. We resolved all disagreements by discussion without the need for a third review author. We sought further information from trial authors if the article contained insufficient data to make a decision about eligibility. We designed a trial eligibility form for trials of red cell transfusions to help in the assessment of relevance, which included ascertaining whether the participants had SCD, and whether the two groups could be defined in the trial on the basis of a transfusion strategy. We recorded the

reasons why potentially-relevant trials failed to meet the eligibility criteria.

Data extraction and management

We updated the data extraction from the data extraction performed for the previous version of this review (Hirst 2012). Since the previous review version, we have now included data extraction for one new trial and updated the data extraction and risk of bias assessment for all included trials. Two review authors (PF, LE) conducted the data extraction according to the guidelines proposed by Cochrane (Higgins 2011a). We resolved disagreements between the review authors by consensus. The review authors were not blinded to names of authors, institutions, journals, or the outcomes of the trials. The data extraction forms were piloted on one trial, thereafter the two authors (PF, LE) extracted data independently for all the trials.

We used the available tables in Review Manager 5 (Review Manager 5.3) to present extracted data on trial characteristics. We extracted the following data.

General information

Review author's name, date of data extraction, study ID, first author of trial, author's contact address (if available), citation of paper, objectives of the trial.

Trial details

Trial design, location, setting, sample size, power calculation, treatment allocation, inclusion and exclusion criteria, reasons for exclusion, comparability of groups, length of follow up, stratification, stopping rules described, statistical analysis, results, conclusion, and funding.

Characteristics of participants

Age, gender, total number recruited, total number randomised, total number analysed, types of underlying disease, lost to follow-up numbers, dropouts (percentage in each arm) with reasons, protocol violations, previous treatments, current treatment, prognostic factors.

Interventions

Experimental and control interventions, method of red cell transfusion (top-up, partial or full exchange transfusion), haemoglobin S levels.

Assessment of bias

Sequence generation, allocation concealment, blinding (participants, personnel, and outcome assessors), incomplete outcome data, selective outcome reporting, other sources of bias.

Outcomes measured

- Perioperative mortality (all-cause);
- serious complications related to sickle cell disease, surgery, or transfusion e.g. acute chest syndrome, cerebrovascular accident, painful crisis, infections, fall in haemoglobin levels;
- other transfusion-related complications, including alloimmunisation, infection from blood products, procedural complications and transfusion reactions;
- length of stay (intensive care unit and inpatient stay);
- quality of life (mobility, ability to work or attend school, self-reliance or as measured on a validated scale);
- measures of organ damage (postoperative difference from baseline) e.g. creatinine (kidney function), liver function tests, lung function tests;
- haemoglobin level and haemoglobin S percentage (pre-transfusion, post-transfusion and postoperative);
- number of units or volume (mL) of red cells infused and, where known for exchange transfusions, volume of blood venesected, with haematocrit.

We used both full-text versions and abstracts to retrieve the data. We used one data extraction form per trial, regardless of number of publications relating to that trial. Where these sources did not provide sufficient information, we contacted authors and trial groups for additional details.

One review author entered data into Review Manager 5 (Review Manager 5.3) and a second review author checked these for accuracy; a statistician validated the data.

Assessment of risk of bias in included studies

We updated the risk of bias assessments from those in the previous versions of this review (Hirst 2012).

Two review authors (LE, PF) assessed all included trials for possible risk of bias (as described in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011c). The assessment included information about the design, conduct and analysis of the trial. We evaluated each criterion using the Cochrane three-point scale (low, high, or unclear risk of bias) in the following areas.

- Selection bias (random sequence generation and allocation concealment)
- Performance bias (blinding of participants and personnel)
- Detection bias (blinding of outcome assessment)
- Attrition bias (incomplete outcome data)
- Reporting bias (selective reporting)
- Other bias

If disagreement arose on the assessment of quality of an included trial, we reached a consensus by discussion, without the need for a third reviewer.

Measures of treatment effect

For continuous outcomes we recorded the mean, standard deviation (SD) and total number of participants in both the treatment and control groups. For dichotomous outcomes we recorded the number of events and the total number of participants in both the treatment and control groups.

For continuous outcomes using the same scale, we performed analyses using the mean difference (MD) with 95% confidence intervals (CIs). There were no continuous outcomes measured using different scales (when we would have used the standardised MD). For dichotomous outcomes we reported the pooled risk ratio (RR) with a 95% CI. Where the number of observed events was small (less than 5% of sample per group), and where trials have balanced treatment groups, we reported the Peto odds ratio (OR) with 95% CI (Deeks 2011). If data allowed, we undertook quantitative assessments using Review Manager 5 (Review Manager 5.3). If we could not report the available data in any of the formats described above, we performed a narrative report, and if appropriate we presented the data in tables.

Unit of analysis issues

It was not specified in the previous versions of this review how to deal with any unit of analysis issues (Hirst 2001; Hirst 2012). There were unit of analyses issues in two trials (Howard 2013; Vichinsky 1995).

In the Vichinsky trial, 50 participants were randomised more than once (Vichinsky 1995). We contacted the authors of the trial as well as the funding source, National Heart, Lung and Blood Institute (NHLBI), requesting patient specific data but we received no response. We report data for individual procedures or outcomes from subsequent publications where we were sure there would only be one patient report (i.e. cholecystectomy and tonsillectomy and adenoidectomy).

Two participants in the TAPS trial were re-randomised; however, we were able to acquire individual data and our reporting on the trial excludes the two re-randomised participants, except in the quality of life analysis where one re-randomised patient in the preoperative transfusion group is included in the final assessment (Howard 2013).

Dealing with missing data

We dealt with missing data according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). Where information was missing or unclear, we contacted the primary investigator or where applicable the funding source.

In order to allow an intention-to-treat analysis, irrespective of later exclusion (regardless of cause) or loss to follow up, we collected data by allocated treatment groups.

Assessment of heterogeneity

If trials were considered sufficiently homogenous in their design, we conducted a meta-analysis and assessed the statistical heterogeneity (Deeks 2011). We assessed statistical heterogeneity of treatment effects between trials using a Chi² test with a significance level at $P < 0.1$ and used the I² statistic to quantify possible heterogeneity (I² value greater than 50% moderate heterogeneity, I² value greater than 75% considerable heterogeneity). If statistical heterogeneity was considerable, we did not report the overall summary statistic.

We could not assess potential causes of heterogeneity by sensitivity analyses due to the lack of data (Deeks 2011).

Assessment of reporting biases

We did not perform a formal assessment of potential publication bias (small trial bias) by generating a funnel plot and statistically test using a linear regression test (Sterne 2011) as no meta-analysis contained 10 or more trials.

Data synthesis

We performed analyses according to Cochrane recommendations (Deeks 2011). We used aggregated data for analysis. For statistical analysis, we entered data into the Review Manager software (Review Manager 5.3).

Where meta-analysis was feasible, we used the fixed-effect model for pooling the data. We used the Mantel-Haenszel method for dichotomous outcomes or Peto method as necessary, and the inverse variance method for continuous outcomes. Where statistical heterogeneity was found to be above 75%, and we then identified a reason for clinical heterogeneity we did not perform a meta-analysis but commented on the results as a narrative.

Even in the absence of statistical heterogeneity, we planned to explore the robustness of any summary measures, particularly with respect to trial methodological quality, but we were unable to perform sensitivity analyses due to inadequate data.

Summary of findings

We used the GRADE approach to build a 'Summary of Findings' table as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011). We used the GRADE approach to rate the quality of the evidence as 'high', 'moderate', 'low', or 'very low' using the five GRADE considerations.

1. Risk of bias: not serious; serious; or very serious.
2. Inconsistency: not serious; serious; or very serious.
3. Indirectness: not serious; serious; or very serious.
4. Imprecision: not serious; serious; or very serious.
5. Publication bias: undetected; or strongly suspected.

We reported separate 'Summary of findings' tables for aggressive preoperative transfusion versus conservative preoperative transfusion; and preoperative transfusion versus no preoperative transfusion. For aggressive preoperative transfusion versus conservative

preoperative transfusion we reported data from the subset with the largest number of participants (cholecystectomy). We made this decision when we identified unit of analysis issues with re-randomisation and neither the authors nor the funding source responded to our request for patient-specific data.

Outcomes included

1. Mortality
2. Acute chest syndrome
3. Painful crisis
4. Serious infection
5. Perioperative-related complications
6. Transfusion-related complications
7. Quality of life

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses on the following characteristics, if appropriate:

- type of surgery;
- severity of the disease;
- age of the participant (paediatric, adults, older adults (over 60 years)).

Due to lack of data, and inconsistent age groupings, only the type of surgery subgroup was performed for the aggressive versus conservative preoperative transfusion comparison.

Investigation of heterogeneity between trials also included, if appropriate:

- age of the trial (as treatment of SCD has changed with the use of hydroxyurea)
- type of transfusion (top-up, partial or full exchange)

Due to lack of data, we found no heterogeneity associated with these factors, but commented on results as a narrative.

If the data had been available, we would have grouped outcome data, with the exception of transfusion-related complications, into those measured during surgery and at three hours, 24 hours, one week and one month after surgery.

Sensitivity analysis

We planned to use the random-effects model for sensitivity analyses as part of the exploration of heterogeneity.

- Including only those trials with a 'low risk of bias' (e.g. RCTs with methods assessed as low risk for random sequence generation and concealment of treatment allocation)
- Including only those trials with less than a 20% dropout rate

We could not do sensitivity analyses due to inadequate data.

RESULTS

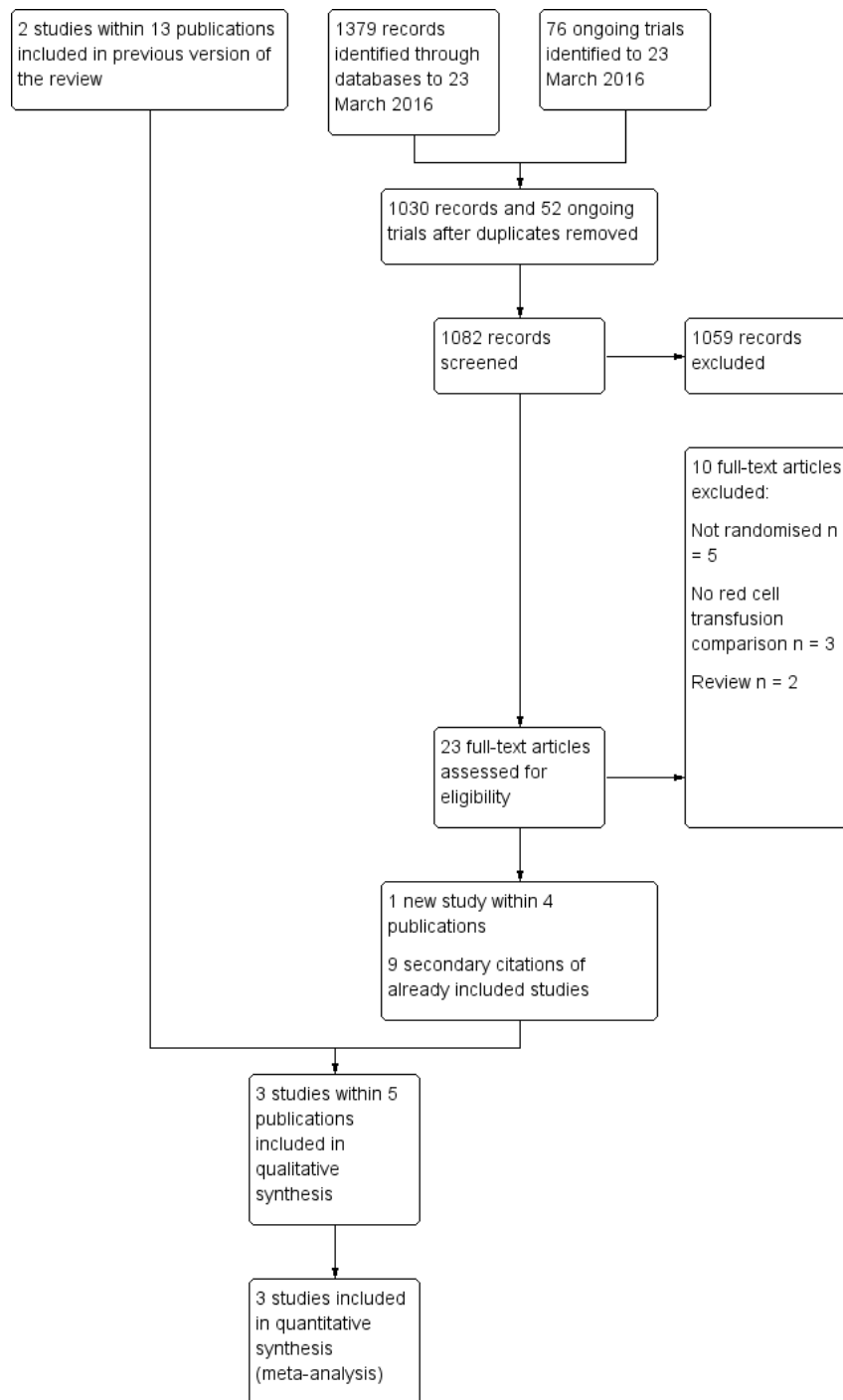
Description of studies

See [Characteristics of included studies](#) and [Characteristics of excluded studies](#).

Results of the search

See PRISMA flow diagram ([Figure 1](#)).

Figure 1. Study flow diagram.



The previous version of this systematic review (Hirst 2012) the review authors identified three trials; two that were completed (Al-Jaouni 2006; Vichinsky 1995) and one that was ongoing (Howard 2013).

In the searches for this update we identified a total of 1455 potentially relevant citations. There were 1082 citations after we removed duplicates, two review authors (PF, LE) excluded 1059 citations on the basis of the abstract, and two authors (PF, LE) reviewed 23 full text articles for relevance. We excluded 10 citations that were not relevant, and identified one trial within four publications (Howard 2013) and nine citations related to previously included trials (Al-Jaouni 2006; Vichinsky 1995).

For this 2016 update, the previous ongoing trial has been included in the review and there are now three trials included (Al-Jaouni 2006; Howard 2013; Vichinsky 1995), we found no ongoing trials.

Included studies

See [Characteristics of included studies](#) for full details of each trial. Three trials, including 990 participants, met the predefined inclusion criteria (Al-Jaouni 2006; Howard 2013; Vichinsky 1995).

Trial design

We included two RCTs (Howard 2013; Vichinsky 1995) and one quasi-RCT (Al-Jaouni 2006). All three trials were multicentre, ranging from two centres (Al-Jaouni 2006) to 36 centres (Vichinsky 1995).

In the Al-Jaouni trial, participants were allocated to receive either preoperative transfusion (simple or partial exchange transfusion) in one hospital versus no preoperative transfusion in the other hospital on alternating days (Al-Jaouni 2006). The length of post-surgery follow up was not reported. In the Howard trial, participants were followed up for 30 days post-surgery with some secondary outcome data collected up to three months after surgery (Howard 2013). In the Vichinsky trial, complications were reported from time of enrolment throughout a 30-day post-surgery follow-up period (Vichinsky 1995).

Trial size

The numbers of participants enrolled in all trials ranged between 70 (Howard 2013) and 551 (Vichinsky 1995). Al-Jaouni enrolled 369 participants over a five-year period (Al-Jaouni 2006). Howard calculated that a sample size of 405 participants would be required to provide 90% power at a 5% significance level to detect a 10% difference in complication rates in either direction (Howard 2013). The trial was stopped after 70 participants had been recruited due to a higher number of people developing an acute chest syndrome in the no preoperative transfusion arm.

Setting

The two RCTs were published in 1995 and 2013 (Howard 2013; Vichinsky 1995), the quasi-RCT was published in 2006 (Al-Jaouni 2006). One trial was based in the USA (Vichinsky 1995); one in Saudi Arabia (Al-Jaouni 2006) and one was a multinational trial in 22 centres in Canada, Ireland, Netherlands and the UK (Howard 2013).

Participants

All trials included individuals with predominantly HbSS disease. The Vichinsky trial only included people with HbSS disease which was confirmed by electrophoresis (Vichinsky 1995). In the Howard trial two (3%) participants were HbS β^0 , both were in the preoperative transfusion group (Howard 2013). In the Al-Jaouni trial 20% of participants were classified as HbS β^0 , 4% were classified as HbS β^+ , and 2% were classified as HbSC (Al-Jaouni 2006). Al-Jaouni stated that all types of surgical procedures were included except for cardiac surgery (Al-Jaouni 2006). In the Howard trial participants were scheduled to undergo low-risk or medium-risk elective surgery under general or regional anaesthesia (Howard 2013). Those scheduled to undergo high risk surgery such as cardiovascular or brain surgery were excluded. Similarly in the Vichinsky trial, participants were undergoing elective surgery and most surgeries were classed as low or medium risk surgery (Vichinsky 1995). One surgery in the aggressive transfusion group was classed as high risk.

In the Al-Jaouni trial, the mean age was 16 years old, age ranges from one to 35 years (Al-Jaouni 2006); in the Howard trial, ages ranged from zero to 40 years or older with only 9% of participants in the 40 years or older age group (Howard 2013); and in the Vichinsky trial, ages ranged from zero to 20 years or older with approximately 75% of participants in the zero to 19 year age group (Vichinsky 1995). In both the Howard and Vichinsky trials, participants were equally divided between males and females (Howard 2013; Vichinsky 1995) and in the Al-Jaouni trial, approximately 60% of the participants were female (Al-Jaouni 2006).

Al-Jaouni reported no severity of disease measures or previous complications (Al-Jaouni 2006). Howard reported the American Society of Anesthesiologists (ASA) risk score for mild, moderate, or severe systemic disease with 67% of participants having mild to moderate disease; also, 70% of participants in the no transfusion group and 56% of participants in the preoperative transfusion group had no history of SCD complications (Howard 2013). In the Vichinsky trial, more participants in the aggressive transfusion group had a history of cardiac disease, smoking or central nervous system disease, although only the latter was statistically significant ($P = 0.049$) and participants were equally divided in both groups between mild-moderate and severe disease on the ASA risk score

(Vichinsky 1995). Two participants in the aggressive transfusion group and one in the conservative transfusion group were classified as having incapacitating illness that is a constant threat to life.

Intervention

The Al-Jaouni and Howard trials compared no preoperative transfusion to preoperative simple or partial exchange transfusion (Al-Jaouni 2006; Howard 2013). Transfusions were allowed during surgery to compensate for blood loss.

In the Vichinsky trial, the surgical procedure was randomised into two groups for preoperative transfusion: aggressive, designed to decrease the haemoglobin S level to less than 30% (Group one); and conservative, which was designed to increase the haemoglobin level to 100 g/L (Group two) (Vichinsky 1995). Blood was from Hb SS negative donors, and participants with a history of allergic reactions to transfusion received leuco-depleted blood. In Group one, 57% of participants received exchange transfusions and 30% had repeated transfusions. In contrast, 77% of participants in Group two received a single transfusion.

Outcomes

Although primary or secondary outcomes were not pre-specified in the Al-Jaouni trial, complications were reported in both groups (Al-Jaouni 2006).

In the Howard trial the primary outcome was the proportion of participants with clinically important complications between randomisation and 30 days afterward (Howard 2013). Clinically important complications were classified as being related to SCD, infection, surgery, or transfusion. Secondary outcomes included the total number of inpatient days, number of red-cell units received during and after surgery; readmission or non-discharge by 30 days after surgery; and a composite outcome of the primary outcome

and alloimmunisation at three months after surgery. Limited quality of life data were also collected.

In the Vichinsky trial, the primary outcome was to compare the rates of perioperative complications (Vichinsky 1995). Complications were recorded and classified as minor (brief temperature elevations and mild wound infections), serious (complications requiring prolonged hospitalisations), or life threatening. Specifically-defined complications included alloimmunisation, painful crisis, acute chest syndrome, neurological events, renal complications and fever or infection. Data regarding transfusion-related complications were also collected. Results were presented as a percentage of each group of operations.

Funding source

Two of the three trials received government funding (Howard 2013; Vichinsky 1995). No funding source was reported in the Al-Jaouni trial (Al-Jaouni 2006).

Excluded studies

We excluded 10 studies primarily because there was no red cell transfusion arm or the study was not randomised (*see Characteristics of excluded studies*).

- Five studies were not randomised (Aziz 2011; El-Shafei 1995; Orringer 1995; Wali 2003).
- Three studies did not assess a red cell transfusion intervention (Daigavane 2013; Koshy 1988; Styles 2007).
- Two studies were reviews (Alotaibi 2014; Debaun 2007).

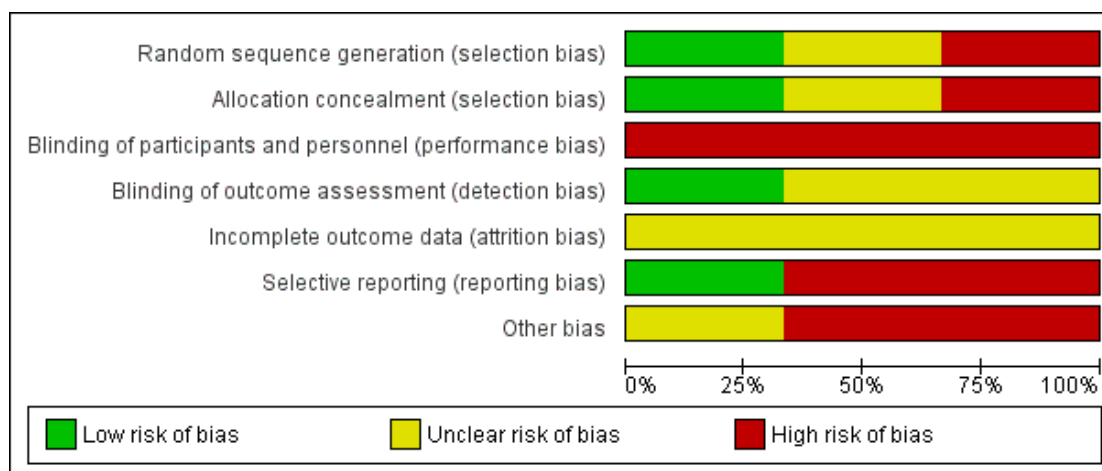
Risk of bias in included studies

Refer to the figures section of the review for visual representations of the assessments of risk of bias across all trials and for each item in the included trials (Figure 2; Figure 3). See the risk of bias section in the *Characteristics of included studies* section for further information about the bias identified within the individual trials.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Al-Jaouni 2006	⊖	⊖	⊖	?	?	⊖	⊖
Howard 2013	⊕	⊕	⊖	⊕	?	⊕	?
Vichinsky 1995	?	?	⊖	?	?	⊖	⊖

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included trials.



Allocation

Random sequence generation

We considered the Howard trial to be at low risk of bias due to generation of the random sequence using prepared lists of random treatment allocations in varying block sizes within each strata (Howard 2013). We assessed the Vichinsky trial as having an unclear risk of bias because the method of randomisation was not reported (Vichinsky 1995). We judged that the Al-Jaouni trial was at a high risk of bias due to the quasi-randomisation method of using alternating days between hospitals (Al-Jaouni 2006).

Allocation concealment (selection bias)

We considered the Howard trial to be at a low risk of bias due to allocation concealment because randomisation was via a centralised, computerised randomisation service (Howard 2013). We assessed the Vichinsky trial to be at an unclear risk of bias because no description of allocation concealment was provided (Vichinsky 1995). We judged the Al-Jaouni trial to be at a high risk of bias because of the mechanism of alternating assignment to transfusion or no transfusion (Al-Jaouni 2006).

Blinding

Blinding of participants and personnel (performance bias)

We judged all three trials to be at low risk of performance bias for all-cause mortality and at high risk of performance bias for all other outcomes as all were open-label trials (Al-Jaouni 2006; Howard 2013; Vichinsky 1995).

Blinding of outcome assessment (detection bias)

We considered the Howard trial to be at low risk of detection bias because all complications were assessed by an independent review panel unaware of treatment allocations (Howard 2013). The remaining trials were at an unclear risk of detection bias as there was no description of blinding of outcome assessors (Al-Jaouni 2006; Vichinsky 1995).

Incomplete outcome data

We considered the Howard trial to be at low risk of attrition bias as an intention-to-treat analysis was used and all enrolled participants were accounted for in the analysis (Howard 2013). We considered the remaining two trials to be at unclear risk of attrition bias (Al-Jaouni 2006; Vichinsky 1995).

In the Vichinsky trial, although an intention-to-treat analysis was used, of the original data collected on 692 surgical procedures, which had been randomly allocated, N = 88 (12.7%) were subsequently excluded due to cancellation of the surgery, diagnostic

error or refusal of the individual to participate (Vichinsky 1995). The Al-Jaouni trial provided no details on intention-to-treat analysis, patient flow and withdrawals or exclusions (Al-Jaouni 2006).

Selective reporting

We considered the Howard trial to be at low risk of reporting bias because the protocol was provided by the authors and all outcomes were reported (Howard 2013). We considered the remaining two trials to be at high risk of selective reporting bias (Al-Jaouni 2006; Vichinsky 1995).

We assessed the Vichinsky trial to be at high risk of selective reporting bias because no protocol was available and some outcome categories with the highest proportion of complications are vaguely described as other, miscellaneous or any complications. Moreover, serious or life threatening complications are reported as a proportion of operations with these complications which is not informative in terms of the number of participants experiencing complications (Vichinsky 1995). In the Al-Jaouni trial, the outcomes reported do not inform all the purported aims of the trial, and some of the outcomes are reported very generally, therefore we assessed this to be at high risk of reporting bias (Al-Jaouni 2006).

Other potential sources of bias

We considered one trial to have an unclear risk of other bias (Howard 2013). The Howard trial was stopped early due to increased harm in the no transfusion group (Howard 2013). The trial did not achieve power to detect differences between arms and so it is unclear how early stoppage may have affected overall results. We considered two trials to have a high risk of bias for other risk of bias (Al-Jaouni 2006; Vichinsky 1995). The Al-Jaouni trial was poorly reported and lacked information on the conduct of the trial and participants, and reported no funding support or conflicts of interest (Al-Jaouni 2006). We judged the Vichinsky trial to have a high risk as outcomes and baseline characteristics are reported by surgical procedures and N = 50 (9%) of participants were re-randomised (Vichinsky 1995).

Effects of interventions

See: [Summary of findings for the main comparison Aggressive versus conservative blood transfusion for sickle cell disease \(SCD\)](#); [Summary of findings 2 Preoperative blood transfusion versus no transfusion for sickle cell disease \(SCD\)](#)

Aggressive versus conservative blood transfusions

One trial evaluated this comparison (Vichinsky 1995). In this trial, outcomes with the exception of mortality, are expressed as percentages of surgeries (604 surgeries in 551 participants). A total of 50 participants (9%) were re-randomised. As a result only data

from two co-publications which reported outcomes by participants, one reporting on cholecystectomy surgeries, (230 participants) (Haber Kern 1997), and another reporting on tonsillectomy and adenoidectomy surgeries (107 participants) (Waldron 1999) are included in this update. The data from these two publications were not combined as we do not know if any participant underwent both surgeries. Therefore, no combined meta-analysis was performed for the aggressive versus conservative blood transfusion intervention, but results are represented graphically.

Primary outcomes

1. Perioperative mortality (all cause)

In the main trial publication there were two deaths reported (Vichinsky 1995). Both men had received aggressive transfusion therapy prior to splenectomy and hip replacement operations. Both had a history of pulmonary disease and developed respiratory failure after surgical complications which progressed to multi-organ failure and death (Vichinsky 1995).

There were no deaths reported in the cholecystectomy or tonsillectomy and adenoidectomy participant subsets.

2. Serious complications

Sickle cell-related serious complications

There were no differences in the number of sickle cell-related complications (acute chest syndrome, painful crisis, neurological event or renal complication) between the aggressive versus the conservative transfusion arms for either surgical subgroup.

Acute chest syndrome: cholecystectomy subgroup, RR 0.84 (95% CI 0.38 to 1.84) (one trial, 230 participants); tonsillectomy or adenoidectomy subgroup, RR 1.08 (95% CI 0.42 to 2.75) (one trial, 107 participants) (Analysis 1.1).

Painful crisis: cholecystectomy subgroup, RR 0.30 (95% CI 0.09 to 1.04) (one trial, 230 participants); tonsillectomy or adenoidectomy subgroup, RR 6.12 (95% CI 0.30 to 124.56) (one trial, 107 participants) (Analysis 1.1).

Neurological event: cholecystectomy subgroup: no events reported; tonsillectomy or adenoidectomy subgroup: no events reported).

Renal complication: cholecystectomy subgroup, RR 0.36 (95% CI 0.01 to 8.83) (one trial, 230 participants); tonsillectomy or adenoidectomy subgroup: no events reported.

Infection-related serious complications

There were no differences in any infection-related complications between the aggressive versus the conservative transfusion arms: cholecystectomy subgroup, RR 1.75 (95% CI 0.59 to 5.18) (one trial, 230 participants); tonsillectomy or adenoidectomy subgroup, RR 2.46 (95% CI 0.47 to 12.85) (one trial, 107 participants) ([Analysis 1.2](#)).

Fever or infection was defined as a temperature of greater than 38.5° C or documented infection lasting at least 48 hours and not attributed to acute chest syndrome.

Perioperative serious complications

A fall in haemoglobin and respiratory events (excluding acute chest syndrome) were not reported for either subgroup.

Intraoperative blood loss was only reported for the tonsillectomy or adenoidectomy subgroup and was not reported by treatment arm. Eight participants experienced excessive blood loss, with a median blood loss of 250 mL (range 150 mL to 500 mL).

There were no differences in any surgery-related complications between the aggressive versus the conservative transfusion arms (cholecystectomy subgroup; RR 0.75 (95% CI 0.36 to 1.55) (one trial, 230 participants); tonsillectomy or adenoidectomy subgroup, RR 1.23 (95% CI 0.50 to 3.03) (one trial, 107 participants) ([Analysis 1.3](#)).

Postoperative serious complications

There were no differences in any surgery-related postoperative complications between the aggressive versus the conservative transfusion arms (only reported in cholecystectomy subgroup, RR 0.87 (95% CI 0.24 to 3.17) (one trial, 230 participants) ([Analysis 1.4](#))

There were no differences in any miscellaneous postoperative complications between the aggressive versus the conservative transfusion arms (cholecystectomy subgroup, RR 0.27 (95% CI 0.03 to 2.40) (one trial, 230 participants); tonsillectomy or adenoidectomy subgroup, RR 3.69 (95% CI 0.40 to 34.32) (one trial, 107 participants) ([Analysis 1.4](#)).

Transfusion-related serious complications

Transfusion-related complications were reported but it was not clear whether any of the transfusion complications reported were serious, therefore we reported them in the following section.

Secondary outcomes

1. Other transfusion-related complications

There was a higher risk of developing a new alloantibody in the aggressive transfusion group (only reported in cholecystectomy subgroup, RR 3.05 (95% CI 1.14 to 8.20) (one trial, 230 participants) ([Analysis 1.5](#)).

There were no differences in the number of transfusion reactions between the aggressive versus the conservative transfusion arms (only reported in cholecystectomy subgroup, RR 2.18 (95% CI 0.77 to 6.18) (one trial, 230 participants) ([Analysis 1.5](#)).

There were no differences in the number of any transfusion complications between the aggressive versus the conservative transfusion arms (cholecystectomy subgroup, RR 1.85 (95% CI 0.89 to 3.88) (one trial, 230 participants); tonsillectomy or adenoidectomy subgroup, RR 3.69 (95% CI 0.78 to 17.45) (one trial, 107 participants) ([Analysis 1.5](#)).

2. Length of stay

Not reported in either subgroup.

3. Quality of life

Not reported in either subgroup.

4. Measures of organ damage

Not reported in either subgroup.

5. Haemoglobin level and haemoglobin S percentage (pre-transfusion, post-transfusion and postoperative)

Haemoglobin level

Pre-transfusion haemoglobin level and postoperative haemoglobin level were not reported in either subgroup.

Post-transfusion haemoglobin level was only reported in cholecystectomy subgroup. There was no difference in the haemoglobin level between the aggressive and conservative transfusion arms, MD 3.00 g/L (95% CI -0.10 to 6.10) (one trial, 230 participants) ([Analysis 1.6](#)).

Haemoglobin S percentage

Pre-transfusion haemoglobin S and postoperative haemoglobin S were not reported in either subgroup.

Post-transfusion haemoglobin S percentage was only reported in cholecystectomy subgroup. There was a much lower haemoglobin S percentage in the aggressive transfusion arm than the conservative transfusion arm, MD -27.00% (95% CI -31.02 to -22.98) (one trial, 230 participants) ([Analysis 1.7](#)).

6. Volume of blood transfused

There was an increase in the number of red cell units transfused in the aggressive transfusion arm compared to the conservative transfusion arm (only reported in cholecystectomy subgroup, MD 2.70 units (95% CI 2.10 to 3.30) (one trial, 230 participants) ([Analysis 1.8](#)).

Preoperative blood transfusion versus no transfusion

Two trials evaluated this comparison ([Al-Jaouni 2006](#); [Howard 2013](#)).

Primary outcomes

1. Perioperative mortality (all cause):

There were no deaths in either trial (two trials, 434 participants).

2. Serious complications

We judged the Al-Jaouni trial to be at high risk of bias ([Al-Jaouni 2006](#)). However, in all instances of sickle cell complications, CIs are wide due to small sample and effect sizes indicating imprecise and inconsistent effects due to insufficient evidence. Similarly, perioperative-, surgery- and transfusion-related serious adverse events analyses have wide CIs indicating imprecise effects due to small sample sizes and low event rates. The Al-Jaouni trial reported very few complications overall but reports a high incidence of circulatory overload in the preoperative transfusion group ([Al-Jaouni 2006](#)), whereas there were no incidences of circulatory overload in the Howard trial ([Howard 2013](#)). However, the Al-Jaouni trial was quasi-randomised with a high risk of bias ([Al-Jaouni 2006](#)), whereas outcome reporting was considered at low-risk of bias in the Howard trial.

Sickle cell related serious complications

Acute chest syndrome

There were more incidences of sickle cell-related serious adverse events, particularly acute chest syndrome in the no preoperative transfusion group in the Howard trial, which fulfilled the criteria for trial stoppage in an interim analysis by the independent data monitoring committee ([Howard 2013](#)). In the Al-Jaouni trial there were more incidences of sickle-related adverse events in the preoperative transfusion group resulting in heterogeneity in the comparison with the acute chest syndrome outcome ([Al-Jaouni 2006](#)). A meta-analysis was not performed because of this heterogeneity and concern that we may be comparing populations that have different underlying incidences of acute chest syndrome; the

Al-Jaouni trial was conducted in Saudi-Arabia whereas the Howard trial was conducted in 22 centres in Canada, Ireland, Netherlands and UK ([Al-Jaouni 2006](#); [Howard 2013](#)). For the Al-Jaouni trial there was no difference between groups, RR 4.81 (95% CI 0.23 to 99.61) (one trial, 369 participants) (unpublished data, obtained by correspondence with author) ([Al-Jaouni 2006](#)); there was a higher incidence of acute chest syndrome in the non-transfused group in the Howard trial, RR 0.11 (95% CI 0.01 to 0.80) (one trial, 65 participants) ([Howard 2013](#)) ([Analysis 2.1](#)).

Painful crisis

There was no difference in the number of acute painful crises between those people receiving a preoperative transfusion and those that did not receive a transfusion, Peto odds ratio (OR) 1.91 (95% CI 0.61 to 6.04) (two trials, 434 participants) ([Analysis 2.2](#)).

Neurological complications

There was no difference in the number of neurological complications between those people receiving a preoperative transfusion and those that did not receive a transfusion, Peto OR 7.22 (95% CI 1.24 to 41.94) (two trials, 434 participants) ([Analysis 2.2](#)).

Renal complications

The number of renal complications between those people receiving a preoperative transfusion and those that did not receive a transfusion was only reported in the Howard trial and no events were reported ([Howard 2013](#)).

Infection-related serious complications

In the Howard trial serious infection was defined as septic shock ([Howard 2013](#)). There was no definition provided in the Al-Jaouni trial ([Al-Jaouni 2006](#)).

There was no difference in the number of serious infections between those people receiving a preoperative transfusion and those that did not receive a transfusion, Peto OR 1.29 (95% CI 0.29 to 5.71) (two trials, 434 participants) ([Analysis 2.3](#)).

Perioperative related serious complications

Fall in haemoglobin

Not reported for either trial.

Intraoperative blood loss

This was only reported in the Howard trial (Howard 2013). There was no difference in intraoperative blood loss between those people receiving a preoperative transfusion and those that did not receive a transfusion, RR 0.97 (95% CI 0.06 to 14.85) (one trial, 65 participants) (Analysis 2.4).

Any surgery-related complications

This was only reported in the Howard trial (Howard 2013). There was no difference in perioperative surgical complications between those people receiving a preoperative transfusion and those that did not receive a transfusion, RR 0.24 (95% CI 0.03 to 2.05) (one trial, 65 participants) (Analysis 2.4).

Clinically important perioperative complications reported in the Howard trial included: infection related; adverse perioperative events occurring in operating room or post anaesthesia care unit or recovery room; intraoperative blood loss; cardiovascular events; respiratory events; others (allergic reaction or anaphylactic shock, residual paralysis, drug error, temperature less than 35° C or greater than 38° C, malignant hypothermia) (Howard 2013).

Delayed surgery

This was only reported in the Al-Jaouni trial (Al-Jaouni 2006). There was an increase in the number of people who had surgery delayed between those people receiving a preoperative transfusion and those that did not receive a transfusion, RR 43.32 (95% CI 6.04 to 311.00) (one trial, 369 participants) (Analysis 2.4).

Respiratory events (excluding acute chest syndrome)

There was no difference in respiratory events (excluding acute chest syndrome) between those people receiving a preoperative transfusion and those that did not receive a transfusion, Peto OR 0.97 (95% CI 0.06 to 15.45) (two trials, 434 participants) (Analysis 2.5).

Postoperative related serious complications

Only the Howard trial reported serious postoperative complications (Howard 2013).

Wound complications

There was no difference in the number of people developing wound complications between those people receiving a preoperative transfusion and those that did not receive a transfusion, RR

0.19 (95% CI 0.01 to 3.89) (one trial, 65 participants) (Analysis 2.6).

Other postoperative complications:

Clinically important postoperative complications reported in the Howard trial included: deep venous thrombosis; pulmonary embolism; wound complication; postoperative bleeding; cardiovascular complications; gastrointestinal complication (Howard 2013). No cases of any of these complications occurred in either arm of the trial.

Transfusion-related serious complications

Circulatory overload

In the Al-Jaouni trial, there was an increase in the number of participants developing circulatory overload in the preoperative transfusion arm compared to the no transfusion arm (Al-Jaouni 2006). Meta-analysis was not performed because there were no events in the Howard trial (two trials, 434 participants, five events in the treatment group in the Al-Jaouni trial (Analysis 2.7) (Howard 2013).

Other transfusion complications

Clinically important transfusion-related complications reported in the Howard trial included: acute haemolytic transfusion reaction; acute hyperhaemolysis; delayed transfusion reaction; anaphylactic or severe allergic reaction; transfusion-related acute lung injury; post transfusion purpura; transfusion transmitted infection; and transfusion-related graft versus host disease (Howard 2013). No cases of any of these complications occurred in either arm of the trial.

Al-Jaouni did not report any other serious transfusion-related complications (Al-Jaouni 2006).

Secondary outcomes

1. Other transfusion-related complications

New alloantibody

Only Howard reported on the development of a new antibody (Howard 2013). There was no difference in the number of people developing a new alloantibody between those people receiving a

preoperative transfusion and those that did not receive a transfusion, Peto OR 7.17 (95% CI 0.14 to 361.44) (one trial, 65 participants) (Analysis 2.8).

Any transfusion reactions

There was no difference in the number of people developing an acute transfusion reaction between those people receiving a preoperative transfusion and those that did not receive a transfusion. Meta-analysis was not performed because there were no events in the Howard trial (two trials, 434 participants), two events in the treatment group in the Al-Jaouni trial (Al-Jaouni 2006; Howard 2013) (Analysis 2.9).

2. Length of stay

Only Howard reported on length of stay (Howard 2013). There was no difference in the length of hospital stay between those people receiving a preoperative transfusion and those that did not receive a transfusion, MD -0.60 days (95% CI -2.38 to 1.18) (one trial, 65 participants) (Analysis 2.10).

3. Quality of life

Only Howard reported quality of life (Howard 2013). There was no difference in the mean health-related quality of life score between the preoperative transfusion and those that did not receive a transfusion as measured by the EQ-5D.

Pre-operative, MD -0.03 (95% CI -0.21 to 0.15) (one trial, 35 participants) (Analysis 2.11).

Post-operative, MD -0.01 (95% CI -0.14 to 0.12) (one trial, 28 participants, includes one re-randomised participant in the preoperative transfusion group) (Analysis 2.11).

The trial publication reported that the mean health-related quality of life scores were higher in the transfusion group than in the no transfusion group when controlling for baseline EQ-5D: (MD 0.024, 95% CI -0.093 to 0.141; one trial, 19 participants, includes one re-randomised participant in the preoperative transfusion group) (Howard 2013).

4. Measures of organ damage

No trial reported on levels of organ damage.

5. Haemoglobin level and haemoglobin S percentage (pre-transfusion, post-transfusion and postoperative)

Only Howard reported haemoglobin levels (Howard 2013).

Pre-transfusion haemoglobin levels

Prior to any red cell transfusion the preoperative haemoglobin group had a higher haemoglobin level than the no transfusion

group, MD 4.80 g/L (95% CI 0.31 to 9.24) (one trial, 65 participants) (Analysis 2.12).

Preoperative haemoglobin levels

There was a rise in the haemoglobin levels in the preoperative transfusion group after receiving the planned transfusion, MD 22.60 g/L (95% CI 17.64 to 27.56) (one trial, 55 participants) (Analysis 2.12).

Postoperative haemoglobin levels

Postoperative haemoglobin levels were higher in the preoperative transfusion group, MD 11.90 g/L (95% CI 3.90 to 19.90) (one trial, 34 participants) (Analysis 2.12).

Pre-transfusion haemoglobin S

There was no difference in the haemoglobin S level between the preoperative transfusion and no transfusion arms prior to the transfusion, MD 0.10% (95% CI -2.96 to 3.16) (one trial, 58 participants) (Analysis 2.13).

Post-transfusion haemoglobin S

The post-transfusion haemoglobin S level was only checked in four of the five participants that received an exchange transfusion, MD -37.80% (95% CI -42.47 to -33.13) (one trial, four participants) (Analysis 2.13).

6. Number of units or volume of red cells transfused

Only the Howard trial reported on the number of units or volume of red cells transfused (Howard 2013).

Preoperative transfusion

In the preoperative transfusion group 25 participants received a top-up transfusion (total of 44 red cell units); and five participants received an exchange transfusion (total of 14 red cell units) (Mean 1.93 red cell units per participant (SD 0.83); one trial; 30 participants).

In the no transfusion group, one participant received two red cell units because Hb had dropped to less than 65 g/L prior to the procedure.

Intraoperative/postoperative transfusion

Fewer people in the transfusion group (n = 4) were transfused intraoperatively and postoperatively than in the no transfusion group (n = 12) (intraoperative: preoperative transfusion; one participant, one red cell unit; no transfusion; four participants, eight red cell units) (postoperative: preoperative transfusion, four participants, 10 red cell units; no transfusion, eight participants, 29 red cell units). One participant in the transfusion group had both intraoperative and postoperative transfusions.

For those participants that received a intraoperative or postoperative transfusion (four participants transfusion; 12 participants no transfusion) there was no difference in the number of units administered per transfusion, MD 0.44 (95% CI -2.52 to 3.40) (one trial, 16 participants) ([Analysis 2.14](#)).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Preoperative blood transfusion versus no transfusion for SCD						
Patient or population: people with SCD Settings: hospital inpatients Intervention: preoperative blood transfusion versus no transfusion						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No transfusion	Preoperative blood transfusion				
Mortality Follow up: 0 - 30 days ¹	See comment	See comment	Not estimable	434 (2 trials ²)	See comment	There were no deaths reported in either trial
Serious complications related to SCD - ACS Follow up: 0 - 30 days ¹	See comment	See comment	Not estimable	434 (2 trials ²)	⊕○○○ very low ^{3,4}	In the Howard trial there were more incidences of acute chest syndrome in the no preoperative arm: RR 0.11 (95% CI 0.01 to 0.80) (1 trial, 65 participants) In the Al-Jaouni trial there were more incidences in the preoperative group but no difference overall: RR 4.81 (95% CI 0.23 to 99.61) (1 trial, 369 participants) A meta-analysis was not performed due to heterogeneity

Serious complications related to SCD - painful crises Follow up: 0 - 30 days ¹	19 per 1000	36 per 1000 (11 to 118)	OR 1.91 (0.61 to 6.04)	434 (2 trials ²)	⊕○○○ very low ^{3,4}	
Serious infection Follow up: 0 - 30 days ¹	14 per 1000	18 per 1000 (4 to 75)	OR 1.29 (0.29 to 5.71)	434 (2 trials ²)	⊕○○○ very low ^{3,4}	
Perioperative complications - any surgery-related	125 per 1000	30 per 1000 (4 to 256)	RR 0.24 (0.03 to 2.05)	65 (1 trial)	⊕⊕○○ low ^{4,5}	
Transfusion related complications - any Follow up: 0 - 30 days ¹	0 per 1000	0 per 1000 (0 to 0)	Not estimable	434 (2 trials ²)	See comment	Complication was the development of circulatory overload
Quality of life Follow up: 0 - 3 months ¹	Mean baseline score in the no transfusion group was not stated	Mean health-related quality of life scores were higher in the transfusion group than in the no transfusion group when baseline EQ-5D controlled for: (MD 0.024, 95% CI -0.093 to 0.141) (Data from published trial results)	Not estimable	19 (1 trial ⁶)	See comment	

*The basis for the **assumed risk** is the event rate in the control group. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ACS: acute chest syndrome; **CI**: confidence interval; **MD**: mean difference; **OR**: Peto odds ratio; **RR**: risk ratio; **SCD**: sickle cell disease

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

¹ Length of follow up was not reported in [Al-Jaouni 2006](#).

- ² The [Al-Jaouni 2006](#) was a quasi-randomised trial and randomisation was by alternating days in 2 hospitals.
- ³ We downgraded the quality of evidence by 2 for high risk of selection bias, performance bias, detection bias, reporting bias due to: the quasi-randomisation of [Al-Jaouni 2006](#); lack of blinding of [Al-Jaouni 2006](#) and [Howard 2013](#); and unclear reporting of [Al-Jaouni 2006](#).
- ⁴ We downgraded the quality of evidence by 1 for imprecision due to wide confidence intervals of the pooled estimates and individual trials contributing to this outcome.
- ⁵ We downgraded the quality of evidence by 1 for high risk of performance bias in [Howard 2013](#) due to lack of blinding.
- ⁶ Results include one re-randomised participant.

DISCUSSION

Summary of main results

This Cochrane review aimed to evaluate the literature on the effectiveness and safety of preoperative transfusions in people with sickle cell disease (SCD).

We identified three randomised or quasi-randomised trials that met our inclusion criteria containing a total of 990 participants. These trials were conducted between 1988 and 2011. The majority of participants had HbSS SCD. The majority of surgical procedures were considered of low or intermediate risk for developing sickle cell-related complications.

One randomised trial compared an aggressive transfusion regimen (decreasing sickle haemoglobin to less than 30%, usually via an exchange transfusion) to a simple transfusion regimen (increasing haemoglobin to 100 g/L) (Vichinsky 1995). This trial re-randomised participants and therefore quantitative analysis was only possible on two subsets of data: participants undergoing cholecystectomy (230 participants); and participants undergoing tonsillectomy or adenoidectomy surgeries (107 participants). Data from these subsets were not combined as we do not know if any participant received both surgeries. Results for the largest subgroup (cholecystectomy) are reported here as results for both subgroups were similar but the results for the tonsillectomy or adenoidectomy surgeries were more imprecise.

The findings of the review led to the following main conclusions regarding an aggressive versus conservative preoperative transfusion regimen.

- There was insufficient evidence to detect a difference in all-cause mortality between people receiving a preoperative transfusion regimen to decrease HbS below 30% and decrease anaemia (usually an aggressive regimen), and those that did not. There were no deaths in either subgroup.
- There was no difference in the number of people developing sickle cell-related complications, a serious infection, any perioperative complications, or transfusion-related complications between people receiving transfusions to lower HbS below 30% and decrease anaemia and those receiving transfusions to increase haemoglobin to 100 g/L to decrease anaemia. This lack of difference between the two outcomes may be due to insufficient evidence to detect a difference due to the small number of participants in the trials.
- Quality of life was not reported.

Two trials (one randomised (Howard 2013) and one quasi-randomised (Al-Jaouni 2006)) with 434 participants compared a preoperative transfusion plus standard care to a group receiving standard care. One trial was stopped early because more people in the no transfusion arm developed an acute chest syndrome.

- There was insufficient evidence to detect a difference in all-cause mortality between people receiving preoperative

transfusions and those that did not (there were no deaths in either trial).

- There was significant heterogeneity between the two trials in the number of people developing an acute chest syndrome, this may have been due to inherent differences between the populations in the underlying incidence of acute chest syndrome, a meta-analysis was therefore not performed. One trial showed a reduced number of people developing acute chest syndrome between people receiving preoperative transfusions and those receiving no preoperative transfusions (65 participants; risk ratio (RR) 0.11 (95% CI 0.01 to 0.80)), whereas the other trial did not (369 participants; RR 4.81 (95% CI 0.23 to 99.61)).

- There was an increase in the number of people developing circulatory overload in people receiving preoperative transfusions, this was only seen in the Al-Jaouni trial, there were no events in Howard trial (Al-Jaouni 2006; Howard 2013).

- There was no difference in the number of people developing a vaso-occlusive crisis, a serious infection, any perioperative complications, or quality of life between people receiving preoperative transfusions and those that did not. This lack of difference between the two outcomes may be due to insufficient evidence to detect a difference due to the small number of participants in the trials.

Overall completeness and applicability of evidence

This review provides the most up-to-date assessment of the effectiveness and safety of a preoperative transfusion policy in people with SCD. This 2016 updated review included one additional randomised trial (Howard 2013).

However, the results of this review should not be interpreted without considering the impact of the following factors.

- The trials included in this review range over a 23-year period (1988 to 2011) during which predicted survival rates and supportive care, have changed substantially, and hydroxyurea has been introduced into routine care.
- The findings in this review can not be generalised to people with HbSC disease or HbS β^+ disease. Two trials specifically excluded these individuals (Howard 2013; Vichinsky 1995), and one trial included only nine people with HbSC disease and 14 people with HbS β^+ disease (Al-Jaouni 2006).
- Only a subset of data in the Vichinsky trial could be analysed due to unit of analysis issues with re-randomisation (Vichinsky 1995).
- There are significant differences in the frequency of sickle cell-related complications in people with HbSS disease due to co-inheritance of genetic variants that lead to the persistence of high levels of foetal haemoglobin (HbF) into adulthood. Some people with SCD have exceptionally high levels of HbF. High HbF is associated with generally milder but not asymptomatic disease. Sickle cell anaemia in Saudi Arabia has population

concentrations in the Southwestern and Eastern Provinces. Most affected people from the Eastern Province carry the Saudi-Indian -globin gene-like cluster haplotype and have very high levels of HbF. Those from the Southwestern Province have typical African-derived haplotypes and lower HbF levels, albeit at twice the level of comparable haplotype groups of African descent (Akinsheye 2011; Steinberg 2012). Haemoglobin F levels were not reported in any of the trials.

- Co-inheritance of alpha thalassaemia may reduce the frequency of complications in people with HbSS (Rumaney 2014; Steinberg 2012). This was not reported in any of the trials.
- Only five participants within the Howard trial had a haemoglobin level above 90 g/L which necessitated an exchange transfusion to reduce their HbS percentage below 60% (Howard 2013). Therefore, there are sparse data on the management of people with higher baseline haemoglobins.
- The majority of participants had intermediate or low risk surgery in all three trials.
- All of the included trials were conducted in wealthy Western countries. However, developing countries often do not have the resources to support such an extensive preoperative transfusion programme. The potential risks associated with transfusion therapy are increased in such settings due to a lack of trained staff, modern equipment, sanitary conditions and clean, infection-free blood products (Ansong 2013). Therefore, the risk-benefit ratio will be different in developing countries to those in the included trials, and the results discussed in this review may not be generalisable to this setting.

Quality of the evidence

Overall, the quality of the evidence was rated as low to very low across different outcomes according to GRADE methodology (Summary of findings for the main comparison and Summary of findings 2). This was due to two of the trials being at high or unclear risk of bias, and many of the outcome estimates being imprecise.

Aggressive versus conservative preoperative transfusion regimen

Five outcomes were considered very low-grade quality evidence according to GRADE methodology due to the serious risk of bias of the included trial, indirectness and the serious imprecision of the estimates. These were:

- serious complications related to SCD - acute chest syndrome;
- serious complications related to SCD - painful crisis;
- serious infection;
- perioperative complications (any);
- transfusion-related complications (any).

This was because of a high risk of performance bias and detection bias due to the nature of the intervention and difficulty blinding participants, physicians and outcome assessors. The reason for indirectness is that we could only report the results in cholecystectomy patients due to unit of analysis issues because of re-randomisation. The reason for the imprecision is because of the small number of participants within the trial and the low number of events.

Preoperative transfusion regimen versus no preoperative transfusion regimen

One outcome (perioperative complications (any)) was considered low-grade quality evidence according to GRADE methodology due to the serious risk of bias of the included trial and the serious imprecision of the estimates. This was because of a high risk of performance bias due to the nature of the intervention and difficulty blinding participants and physicians. The reason for the imprecision is because of the small number of participants within the trial and the low number of events.

Two outcomes were considered very low-grade quality evidence according to GRADE methodology due to the very serious risk of bias of the included trials and the serious imprecision of the estimates. These were:

- serious complications related to sickle cell disease - painful crisis;
- serious infection.

This was because of a high risk of performance bias and detection bias due to the nature of the intervention and difficulty blinding participants, physicians and outcome assessors; and a high risk of selection bias due to one quasi-randomised trial. The reason for the imprecision is because of the small number of participants within the trial and the low number of events.

Refer to the figures for visual representations of the assessments of risk of bias across all trials and for each item in the individual trials (Figure 2; Figure 3).

Potential biases in the review process

To our knowledge, our review process is free from bias. We conducted a comprehensive search; searching data sources (including multiple databases, and clinical trial registries) to ensure that all relevant trials would be captured. There were no restrictions for the language in which the paper was originally published. The relevance of each paper was carefully assessed and all screening and data extractions were performed in duplicate. We pre-specified all outcomes and subgroups prior to analysis. There were insufficient numbers of included trials within the meta-analyses for us to use a funnel plot to examine the risk of publication bias.

Agreements and disagreements with other studies or reviews

We know of only one recent systematic review (Alotaibi 2014), and one evidence-based Expert Panel Report (Yawn 2014). The systematic review by Alotaibi included both randomised and non-randomised studies (Alotaibi 2014). The authors included 10 studies for meta-analyses and identified the same three randomised or quasi-randomised trials identified in this review and included another seven observational studies. They used criteria recommended by the US preventive services task force and the Canadian task force on preventive health care for quality assessment, and rated each trial as good, fair, or poor based on internal validity criteria established a priori. They rated the quality of randomised trials from good (Howard 2013) to fair (Al-Jaouni 2006; Vichinsky 1995), and all observational studies were rated as poor. They did not use GRADE methodology to create a 'Summary of findings' table and rate the quality of evidence, nor did they follow Cochrane standards for reporting systematic reviews. They included surgical procedures as the unit of analysis in the Vichinsky trial and did not take into account re-randomisation (Vichinsky 1995).

In accordance with this review, Alotaibi reports a lack of data in individuals with other sickle cell genotypes and in those with HbSC disease (Alotaibi 2014).

In accordance with this review, Alotaibi found no difference between aggressive transfusion and conservative transfusion for all-cause mortality, sickle cell-related complications, (analysed as a composite outcome which included acute chest syndrome, painful crisis and neurological complications), or perioperative complications (Alotaibi 2014). We found no difference in transfusion-related complications between the conservative and aggressive transfusion groups, whereas in Alotaibi, transfusion-related complications were higher in those treated with an aggressive transfusion (Alotaibi 2014). The Alotaibi review included 666 individuals in the analysis but it is not clear how many studies were pooled or if there was any heterogeneity identified (Alotaibi 2014).

In accordance with this review, Alotaibi found no difference between preoperative transfusion and no preoperative transfusion for perioperative mortality, transfusion-related complications and postoperative infections (Alotaibi 2014). It is not reported how many studies were pooled in these analyses and if there was any heterogeneity identified. They also found no differences in the rate of major surgical complications. There was significant heterogeneity among the three included observational studies and also when pooled with the data from the Howard trial, but no explanation for heterogeneity was provided (Howard 2013). In contrast to this review, Alotaibi found no differences between preoperative and no preoperative transfusion in sickle cell-related complications, analysed as a composite outcome (Alotaibi 2014). The analysis showed significant heterogeneity between randomised trials (Al-Jaouni 2006; Howard 2013), and when both randomised and the two included non-randomised studies were pooled. No

explanation for the heterogeneity was provided; however, they did comment that the randomised trials had major quality and power limitations.

Alotaibi also analysed another seven non-randomised studies qualitatively. These were not eligible for meta-analyses and it was reported that preoperative transfusion had a beneficial effect for a reduction in postoperative complications, and a negligible effect in low-risk procedures (Alotaibi 2014).

The 2014 evidence report on the management of SCD by the Expert Panel included randomised trials, non-randomised intervention studies, and observational studies (Yawn 2014). For preoperative red blood cell transfusion they included one randomised trial, four observational studies and six case series. It also included a *post hoc* commentary on the Howard trial and translated the results into a recommendation that red blood cell transfusion should be used in children and adults to increase their Hb levels to 10 g/dL prior to any surgical procedures involving general anaesthesia and rated this as a strong recommendation with moderate quality evidence (Yawn 2014). No recommendations were made regarding type (aggressive or conservative) of transfusion therapy. They make a strong recommendation based on low-quality evidence to consult an SCD expert for guidance as to the appropriate transfusion method for people who have high haemoglobin levels, who are on long-term hydroxyurea therapy or are undergoing high risk surgery. They also make a moderate recommendation with low-quality evidence to consult an SCD expert for those with HbSC or HbSB⁺ undergoing surgical procedures involving general anaesthesia.

AUTHORS' CONCLUSIONS

Implications for practice

It is widely agreed that people with SCD should be warm, well-hydrated and well-oxygenated for surgery in order to avoid conditions that could lead to relative or regional hypoxia, increased sickling and compromised oxygen delivery to tissues.

There is insufficient evidence from randomised trials to determine whether conservative preoperative blood transfusion is as effective as aggressive preoperative blood transfusion in preventing sickle-related or surgery-related complications. Preoperative blood transfusion may prevent development of acute chest syndrome in people with HbSS who are undergoing moderate risk surgery. Due to lack of evidence this review cannot comment on management for people with HbSC or HbS β^+ disease or those with high baseline haemoglobin concentrations, or management of individuals undergoing low-risk surgery.

Implications for research

Although information from a well-designed prospective ran-

domised controlled trial of preoperative blood transfusion in people with SCD is ideal in order to make recommendations for the optimal use of this therapy, there are significant challenges in conducting randomised trials in people with haemoglobinopathies. In the Howard trial, out of 342 people screened only 70 were recruited with reasons for exclusion being decisions by treating clinicians, transfusion within the previous three months, refusal of consent, logistical reasons, low haemoglobin concentration, acute chest syndrome and orthopaedic surgery (Howard 2013). Issues that were not addressed in the included trials includes managing those with low risk surgery, efficacy of a regime of several top-up transfusions over four to six weeks in lieu of exchange transfusions, and the management of people with HBSC or HbS β^+ disease.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Al-Jaouni 2006

Methods	<p>Quasi-RCT. Participants were assigned to either no transfusion or to partial or exchange transfusion on alternating days between two hospitals - in one hospital all participants would receive transfusions and in the other hospital no participants would be transfused</p> <p>Trial conducted over a period of five years from November 1996 to November 2001 at two hospitals in Saudi Arabia</p> <p>Follow up: not stated.</p>
Participants	<p>Quasi-randomisation: 369 participants with sickle cell anaemia.</p> <p>No transfusion (Group I): N = 181.</p> <p>M: 76; F: 105.</p> <p>Age: 1 - 4 years: 15; > 4 - 12 years: 46; > 12 - 18 years: 40; over 18 - 35 years: 80.</p> <p>Phenotype: HbSS: 137; HbSβ^0: 35; HbSβ^+: 5; HbSC: 4.</p> <p>Scheduled surgery: adenotonsillectomy: 52; total hip arthroplasty: 28; cholecystectomy: 27; splenectomy: 28; obstetrics/gynaecological surgeries: 23; miscellaneous: 16; emergency: 7.</p> <p>History of complications: not reported.</p> <p>ASA risk score: not reported.</p> <p>Simple or partial exchange transfusion (Group II): N = 188.</p> <p>M: 78; F: 110.</p> <p>Age: 1 - 4 years: 16; > 4 - 12 years: 42; > 12 - 18 years: 38; > 18 - 35 years: 82.</p> <p>Phenotype: HbSS: 135; HbSβ^0: 39; HbSβ^+: 9; HbSC: 5.</p> <p>Scheduled surgery: adenotonsillectomy: 45; total hip arthroplasty: 21; cholecystectomy: 30; splenectomy: 20; obstetrics/gynaecological surgeries: 35; miscellaneous: 28; emergency: 9.</p> <p>History of complications: not reported.</p> <p>ASA risk score: not reported.</p> <p>Preoperative transfusion type: simple: 90; partial exchange: 98.</p> <p>Inclusion criteria: not reported.</p> <p>Exclusion criteria: not reported.</p>
Interventions	<p>Group I: no preoperative transfusion. In the no transfusion group, transfusion was given only as compensation for blood loss during surgery</p> <p>Group II: preoperative transfusion: included simple or partial exchange transfusion</p> <p>Type of red cell component: not reported.</p>
Outcomes	<p>Primary outcome: not reported but the aim of the trial was to assess the role of preoperative transfusion practice in people with SCA and to assess the new trends and recommendations that haemoglobin concentration is not the sole parameter that should guide transfusion preoperatively</p> <p>Secondary outcomes: not reported.</p> <p>Trial reported on complications and delay of surgery.</p>
Notes	<p>Conflict of interest: no declaration.</p> <p>Funding: not stated.</p>

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	This was a quasi-RCT and participants alternated between being assigned to no transfusion in one hospital and to transfusion in the second hospital every other day. The regimen alternated over a two time scale from 1996 to 1998 and over a one week time scale from 1998 to 2001. The reason for the change in the allocation regimen was not reported
Allocation concealment (selection bias)	High risk	Allocation concealment was not stated but given the quasi-randomised protocol investigators would know in advance which regimen participants would be assigned to depending on the day of the week
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding due to nature of intervention. States that treatment protocol was similar in both hospitals
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was not stated whether an ITT analysis was used. There was no description of participant flow or withdrawals, As well complications are reported but only by Group I or Group II with no total N's reported, although percentages may indicate that complications were reported for all participants albeit reporting reflects one complication per participant
Selective reporting (reporting bias)	High risk	Outcomes were not pre-specified. Complications were reported but very generally - circulatory overload or heart failure, minor respiratory complication, moderate to severe respiratory distress (not clear if includes acute chest syndrome). Also no reporting of complications by disease severity within participants. Also data that are reported do not necessarily support the stated aims of the trial since no haemoglobin con-

		centrations are reported as well as no reporting of intraoperative or postoperative blood transfusions or units of blood transfused in either group
Other bias	High risk	This trial is very poorly reported.

Howard 2013

Methods	<p>Multicentre RCT in 22 centres in Canada, Ireland, Netherlands and UK between November 2007 and March 2011</p> <p>Follow up: participants were followed up for 30 days post-surgery for primary outcomes. Some secondary outcomes were collected up to 3 months after surgery</p>
Participants	<p>Randomisation: individuals screened: N = 343; participants enrolled: N = 70; Overall: N = 67*. 2 individuals were entered into the trial twice.</p> <p>No transfusion: N = 33.</p> <p>M: 17 (52%) F: 16 (48%).</p> <p>Age: 1 - 6: 10 (30%); 7 - 16: 11 (33%); 17 - 39: 11 (33%) \geq 40: 1 (3%).</p> <p>Phenotype: HbSS: 33 (100%) ; HbSβ⁰: 0.</p> <p>Scheduled surgery: medium-risk:all: 28 (85%); abdominal: 13 (39%); ENT: 9 (27%) ; orthopaedic: 4 (12%) other: 2 (6%); low risk: 5 (15%).</p> <p>History of sickle cell complications: N: 23 (70%) Y: 10 (30%).</p> <p>ASA* risk score: 2 (mild systemic disease): 20 (61%); 3 (severe systemic disease): 13 (39%).</p> <p>Preoperative transfusion: N = 34.</p> <p>M: 16 (47%) F: 18 (53%).</p> <p>Age: 1 - 6 years: 8 (24%); 7 - 16 years: 11 (32%); 17 - 39 years: 10 (29%); \geq 40 years: 5 (15%).</p> <p>Phenotype: HbSS: 32 (94%); HbSβ⁰: 2 (6%).</p> <p>Scheduled surgery: medium-risk:all: 26 (77%); abdominal: 10 (29%); ENT: 7 (21%) ; orthopaedic: 6 (18%); other: 3 (9%); low risk: 8 (24%).</p> <p>History of complications: No: 19 (56%); Yes: 15 (44%).</p> <p>ASA risk score: 2 (mild systemic disease): 24 (73%); 3 (severe systemic disease): 9 (27%).</p> <p>Preoperative transfusion type: simple: 25; partial exchange: 5.</p> <p>Inclusion criteria: individuals had haemoglobin SS (HbSS) or haemoglobin Sβ⁰ thalassaemia (HbSβ⁰thal) aged at least one year; scheduled to for low-risk or medium-risk elective surgery under local or general anaesthesia within 28 days</p> <p>Exclusion criteria: participants could not have a blood transfusion within previous 3 months; participants scheduled to undergo high-risk operations such as cardiovascular or brain surgery; haemoglobin levels lower than 65 g/L; history of ACS within previous 6 months or intubation; and mechanical ventilation ever for the treatment of ACS; oxygen saturation lower than 90%; current renal dialysis; history of stroke in children</p> <p>*3 participants randomised in error were not included in the primary ITT analysis as they had no follow-up data</p>

Interventions	No preoperative transfusion: N = 34. Preoperative transfusion: N = 36. Preoperative red cell transfusions were within 10 days of surgery with the aim of increasing haemoglobin levels to 100 g/L. In participants with transfusions lower than 90 g/L top-up transfusion was used. In participants with Hb levels of 90 g/L or higher partial exchange transfusion was used to achieve an HbS percentage less than 60% Type of red cell component: leucocyte-depleted, fully matched for ABO, full Rhesus phenotype (Cc/D/Ee), and K1 antigen, plus any other antigens to which the participant had antibodies	
Outcomes	Primary outcome: proportion of participants with clinically important complications between randomisation and 30 days after surgery. Clinically important complications were classified as being related to SCD, infection, surgery, or transfusion - definitions were provided to trial centres Secondary outcomes: total number of inpatient days; number of red-cell units received during and after surgery, readmission or non-discharge by 30 days after surgery; composite outcome of the primary outcome; alloimmunisation at three months after surgery, quality of life assessments with the EQ-5D	
Notes	The trial was stopped in March 2011 with 70 participants enrolled due to an emerging imbalance in SAEs with a greater proportion of participants with SAEs in the no transfusion group : 10/30 (33%); pre-transfusion group : 1/31 (3%); absolute risk increase: 0.24 (95% CI: 0.04 to 0.43) P = 0.02 ; NNTH = 4. Trial stoppage was recommended by an independent data monitoring committee Conflict of interest: authors declare no conflicts of interest. Funding: trial funded by NHS Blood and Transplant UK.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were allocated treatment by an independent,centralised online randomisation service. Block randomisation was used to avoid centre effects, and participants were stratified by surgical risk (low or medium), age (1 - 6 years, 7 - 16 years, 17 - 39 years, or 40 years or older), and history of complications related to SCD
Allocation concealment (selection bias)	Low risk	Allocation was by a centralised online service independent of the trial investigators
Blinding of participants and personnel (performance bias) All outcomes	High risk	States that the trial was open label and a treatment protocol was provided for centres but not mandatory. Management of participants may have differed between participants receiving and not receiving a preop-

		erative transfusion
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Detailed reports of complications were scrutinised by an independent endpoint review panel that was unaware of treatment allocations to assess whether events satisfied the trial definitions. Complications that were life threatening or resulted in death, permanent or severe disability, or other important medical outcomes were additionally reported as SAEs and were reviewed by the independent data monitoring committee
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Of 70 participants enrolled 3 were randomised in error and, therefore, only 67 participants were included in the ITT analysis N = 33 in the no-preoperative transfusion and N = 34 in the preoperative-transfusion group. Complete quality of life data were only available for 29 participants. Samples for alloimmunisation were only available for 55 participants
Selective reporting (reporting bias)	Low risk	All outcomes reported - secondary outcomes were reported descriptively due to small number of participants
Other bias	Unclear risk	In an unscheduled interim analysis the trial was stopped early because of a recommendation from the independent data monitoring committee due to an increase in SAEs in the no-transfusion group with only 70 participants of a planned sample size of 405 to achieve 90% power 2 participants were included in the trial twice with different trial numbers

Vichinsky 1995

Methods	RCT at 36 centres in the USA between 1988 and 1993. Each institution had a principal investigator, surgeon, anaesthesiologist, data coordinator and nurse assigned to the trial Follow up: participants were followed for complications from time of enrolment to 30 days post-surgery
Participants	*Randomisation: N = 551 participants with homozygous SCD confirmed by electrophoresis - Agressive regimen (Group 1): N = 278

	<p>M: 54% F: 46%.</p> <p>Age: 0 - 9: 40%; 10 - 19: 35% ≥ 20: 25%.</p> <p>ASA risk score: 2 (mild systemic disease): 47%; 3 (severe systemic disease): 51%; 4 (incapacitating constant threat to life): 2%.</p> <p>Surgical risk category:low risk: 26%; medium risk: 73%; high risk: 1%.</p> <p>Most frequent surgeries: cholecystectomy: 36%; ENT: 25%; orthopaedic: 11%; splenectomy: 6%; herniorrhaphy: 5%</p> <p>Preoperative transfusion type: simple: 36%; exchange: 64%.</p> <p>Conservative regimen (Group 2): N = 273.</p> <p>M: 48% F: 52%.</p> <p>Age: 0 - 9 years: 40%; 10 - 19 years: 36%; ≥ 20 years: 24%.</p> <p>ASA risk score: 2 (mild systemic disease): 48%; 3 (severe systemic disease): 51%; 4 (incapacitating constant threat to life): 1%.</p> <p>Surgical risk category:low risk: 23%; medium risk: 77%; high risk: 0%.</p> <p>Most frequent surgeries: cholecystectomy: 41%; ENT: 26%; orthopaedic: 13; splenectomy: 4%; herniorrhaphy: 5%</p> <p>Preoperative transfusion type:not transfused: 2%; simple: 91%; exchange: 7%.</p> <p>Inclusion criteria: diagnosis of sickle cell anaemia documented by the presence of haemoglobin SS on electrophoresis; undergoing elective surgery; had not received a transfusion within 3 months before the surgery</p> <p>Exclusion criteria: not reported.</p> <p>*baseline characteristics are reported as a % of surgical procedures: Group 1: n = 303; Group 2: n = 301</p>	
Interventions	<p>Aggressive regimen: designed to maintain HbS < 30% and haemoglobin level of 100 g/L</p> <p>Conservative regimen: designed to maintainHb > 100 g/L regardless of level of HbS</p> <p>Type of red cell component: the presence of antibodies determined with standard screening techniques and participants received blood from donors who tested negative for haemoglobin SS. Participants with prior febrile reaction to transfusion received leukocyte-depleted red cells</p>	
Outcomes	<p>Primary outcomes: rates of perioperative complications - all complications occurring from the time of enrolment throughout a 30 day follow-up period including death, miscellaneous intraoperative event, ACS, fever or infection, miscellaneous postoperative event, painful crisis, neurological event, renal complication, any complication</p> <p>Secondary outcomes: none stated.</p>	
Notes	<p>Participants with more than one surgery were randomly reassigned to a treatment group for each subsequent procedure</p> <p>Conflict of interest: none declared.</p> <p>Funding: grant from the National Heart Lung and Blood Institute.</p>	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of random sequence generation was not described.

Allocation concealment (selection bias)	Unclear risk	Concealment of allocation was not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label as blinding was not possible for participants and clinicians, but state that a standardised treatment protocol was developed by a multidisciplinary committee
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated that outcome assessment was blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data were analysed according to the ITT principle and once the random assignments had been made the participants remained in their designated groups regardless of their preoperative haemoglobin S values Of the original data collected on 692 randomly allocated surgical procedures, 88 (12.7% of trial procedures) were subsequently excluded due to cancellation of the surgery, diagnostic error or refusal of the individual to participate in the trial, 42 were from Group 1 and 46 from Group 2. While it is stated that the participant characteristics of this group were similar in both groups, and that the age range was representative of the whole sample, the fairly limited information of participant or procedure characteristics including at what point in the randomisation that procedures were excluded, and the high exclusion rate, may introduce some attrition bias
Selective reporting (reporting bias)	High risk	Serious or life threatening complications presented as % of operations with these complications - not informative in terms number of participants with these complications. As well 2 categories with the highest number of % complications are vaguely described as "miscellaneous intraoperative event" and "any complication" Similarly for transfusion-related complications - "Any complication" is largest group but not clear how serious or mild Also with 9% of participants re-randomised, for more surgeries, it is not clear how this would impact the rates

Other bias	High risk	A total of 551 participants were randomly assigned to Group 1 or Group 2 and underwent a total of 604 operations. Participants who had more than one operation were randomly reassigned to a treatment group for each subsequent procedure. Complications by number of surgeries were counted not participants, and 9% of participants were randomised more than once. "Each patient's transfusion history was recorded", N = 50 (9%) had 53 repeated surgeries.
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ACS: acute chest syndrome

ASA: American Society of Anesthesiologists

CI: confidence interval

ENT: ears, nose and throat

Hb: haemoglobin

HbS: sickle cell haemoglobin

ITT: intention-to-treat

RCT: randomised controlled trial

SCA: sickle cell anaemia

SCD: sickle cell disease

SAEs: serious adverse events

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Alotaibi 2014	Review article.
Aziz 2011	Participants were not randomised to treatment groups.
Daigavane 2013	Not a red cell transfusion comparison.
Debaun 2007	Review article.
El-Shafei 1995	Participants were not randomised to treatment groups.
Geoghegan 2015	Participants were not randomised to treatment groups.
Koshy 1988	Not a red cell transfusion arm comparison.
Orringer 1995	Participants were not randomised to treatment groups.

(Continued)

Styles 2007	Not a red cell transfusion comparison
Wali 2003	Participants were not randomised to treatment groups.

DATA AND ANALYSES

Comparison 1. Aggressive versus conservative blood transfusion

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serious complications related to sickle cell disease	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Cholecystectomy acute chest syndrome	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Tonsillectomy and adenoidectomy acute chest syndrome	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Cholecystectomy painful crisis	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Tonsillectomy and adenoidectomy painful crisis	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 Cholecystectomy renal impairment	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Serious infection	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Cholecystectomy	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Tonsillectomy and adenoidectomy	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Perioperative complications	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Cholecystectomy complications (any)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Tonsillectomy and adenoidectomy complications (any)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Postoperative complications	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Cholecystectomy any complication	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Cholecystectomy miscellaneous complications	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Tonsillectomy and adenoidectomy miscellaneous complications	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Transfusion-related complications	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Cholecystectomy new alloantibody	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Cholecystectomy any reactions	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Cholecystectomy complications (any)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.4 Tonsillectomy and adenoidectomy complications (any)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

6 Cholecystectomy preoperative haemoglobin	1	Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7 Cholecystectomy preoperative haemoglobin S	1	Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8 Cholecystectomy volume of blood transfusion/venesection	1	Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Comparison 2. Preoperative blood transfusion versus no transfusion

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serious complications related to sickle cell disease (acute chest syndrome)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Serious complications related to sickle cell disease	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Painful crises	2	434	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.91 [0.61, 6.04]
2.2 Neurological complications	2	434	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.22 [1.24, 41.94]
3 Serious infection	2	434	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.29 [0.29, 5.71]
4 Perioperative complications	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Intraoperative blood loss	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Any surgery-related	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Delayed surgery	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Perioperative complications (respiratory)	2	434	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.06, 15.45]
6 Postoperative complications (wound complications)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7 Transfusion-related complications (serious)	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
7.1 Transfusion-associated circulatory overload	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Transfusion-related complications (new alloantibody)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
9 Transfusion-related complications (transfusion reactions)	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
10 Length of stay	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10.1 Hospital length of stay	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Quality of life	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11.1 Preoperative quality of life	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Postoperative quality of life	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Haemoglobin concentration	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12.1 Pre-transfusion haemoglobin	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

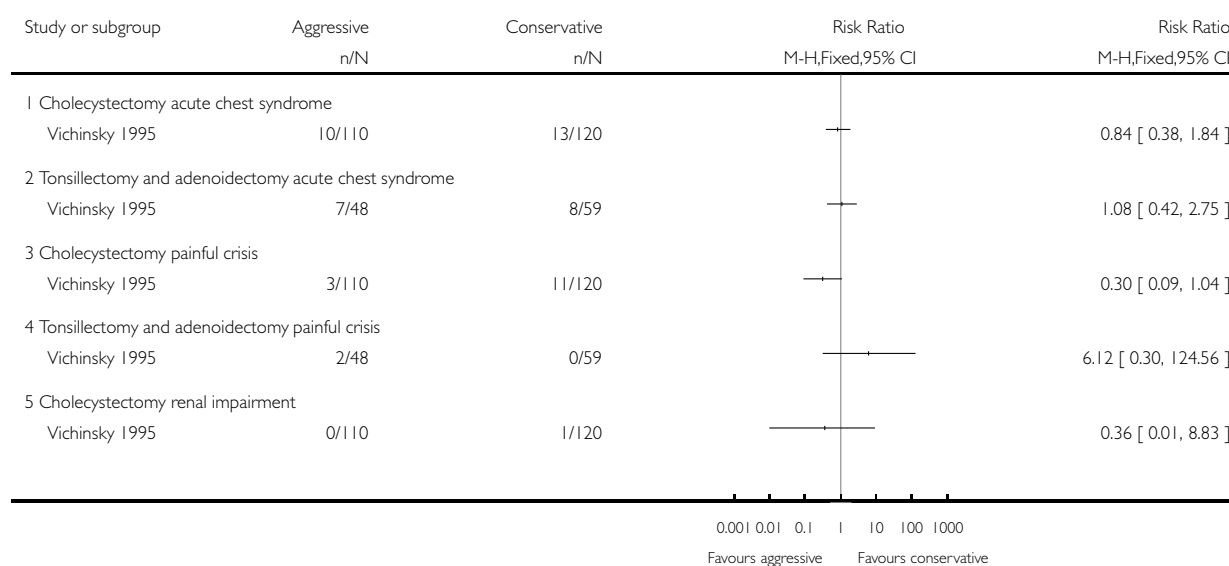
12.2 Post-transfusion haemoglobin	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.3 Postoperative haemoglobin	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Haemoglobin S	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13.1 Pre-transfusion Haemoglobin S	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Post-transfusion haemoglobin S	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Number of units or volume of red cells transfused	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Aggressive versus conservative blood transfusion, Outcome 1 Serious complications related to sickle cell disease.

Review: Preoperative blood transfusions for sickle cell disease

Comparison: 1 Aggressive versus conservative blood transfusion

Outcome: 1 Serious complications related to sickle cell disease

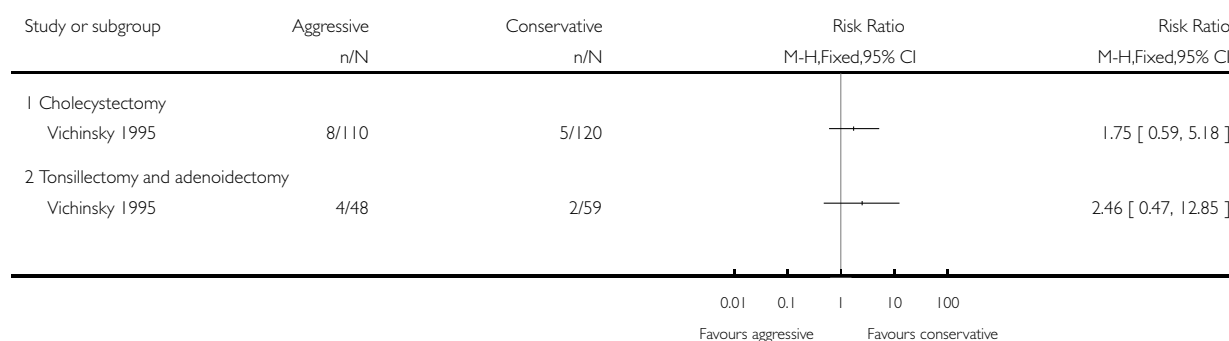


Analysis 1.2. Comparison 1 Aggressive versus conservative blood transfusion, Outcome 2 Serious infection.

Review: Preoperative blood transfusions for sickle cell disease

Comparison: 1 Aggressive versus conservative blood transfusion

Outcome: 2 Serious infection

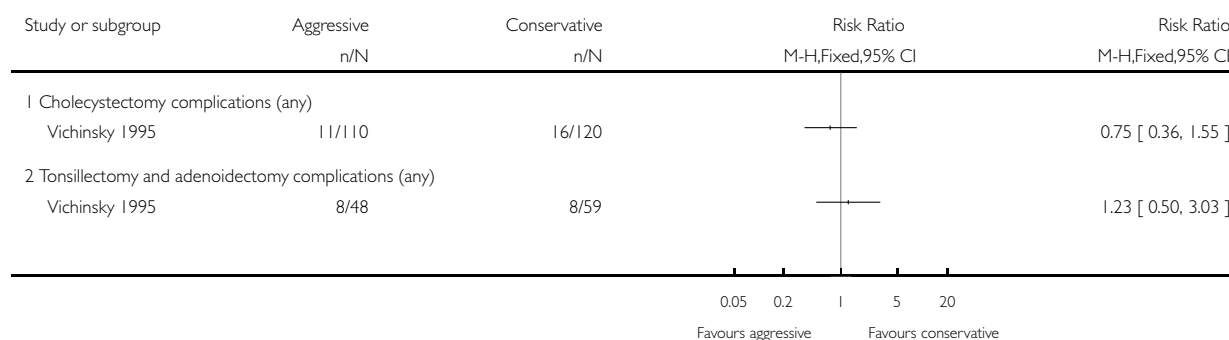


Analysis 1.3. Comparison 1 Aggressive versus conservative blood transfusion, Outcome 3 Perioperative complications.

Review: Preoperative blood transfusions for sickle cell disease

Comparison: 1 Aggressive versus conservative blood transfusion

Outcome: 3 Perioperative complications

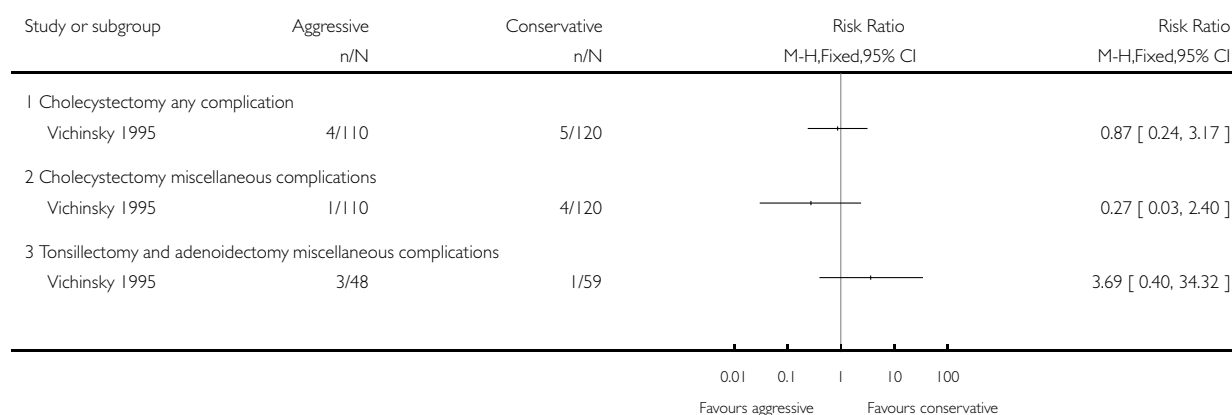


Analysis 1.4. Comparison 1 Aggressive versus conservative blood transfusion, Outcome 4 Postoperative complications.

Review: Preoperative blood transfusions for sickle cell disease

Comparison: 1 Aggressive versus conservative blood transfusion

Outcome: 4 Postoperative complications

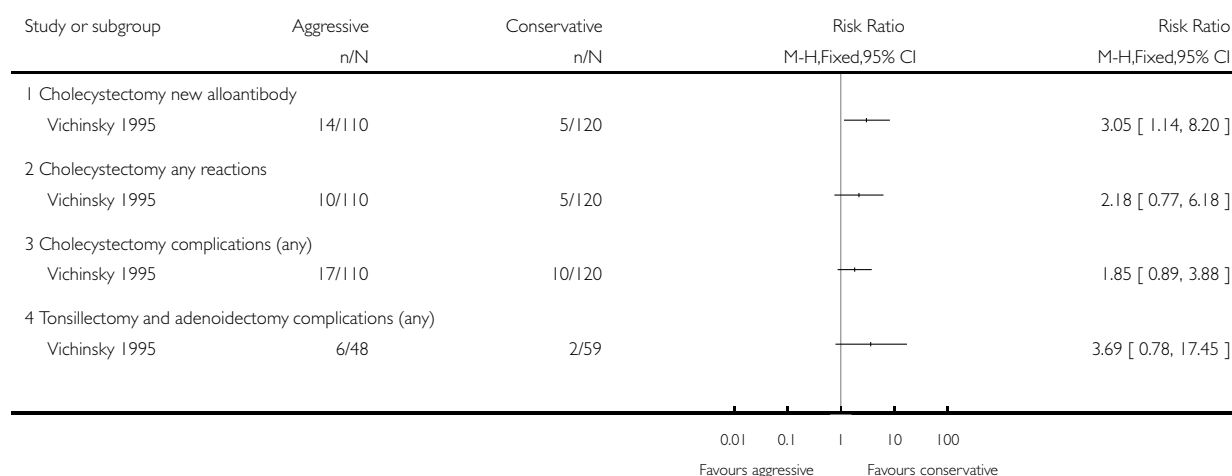


Analysis 1.5. Comparison 1 Aggressive versus conservative blood transfusion, Outcome 5 Transfusion-related complications.

Review: Preoperative blood transfusions for sickle cell disease

Comparison: 1 Aggressive versus conservative blood transfusion

Outcome: 5 Transfusion-related complications

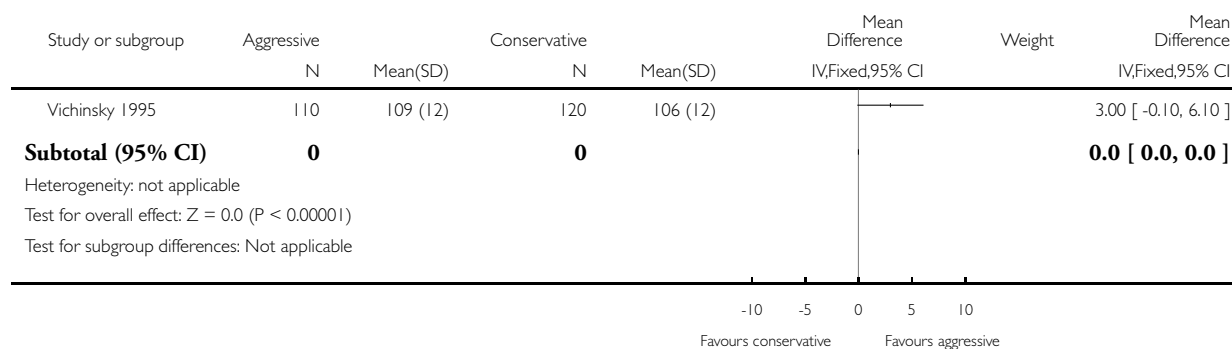


Analysis 1.6. Comparison 1 Aggressive versus conservative blood transfusion, Outcome 6 Cholecystectomy preoperative haemoglobin.

Review: Preoperative blood transfusions for sickle cell disease

Comparison: 1 Aggressive versus conservative blood transfusion

Outcome: 6 Cholecystectomy preoperative haemoglobin

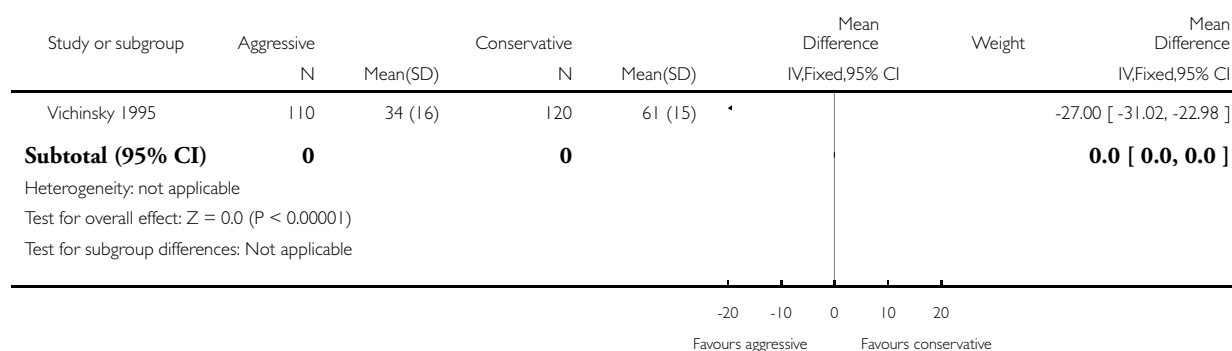


Analysis 1.7. Comparison 1 Aggressive versus conservative blood transfusion, Outcome 7 Cholecystectomy preoperative haemoglobin S.

Review: Preoperative blood transfusions for sickle cell disease

Comparison: 1 Aggressive versus conservative blood transfusion

Outcome: 7 Cholecystectomy preoperative haemoglobin S

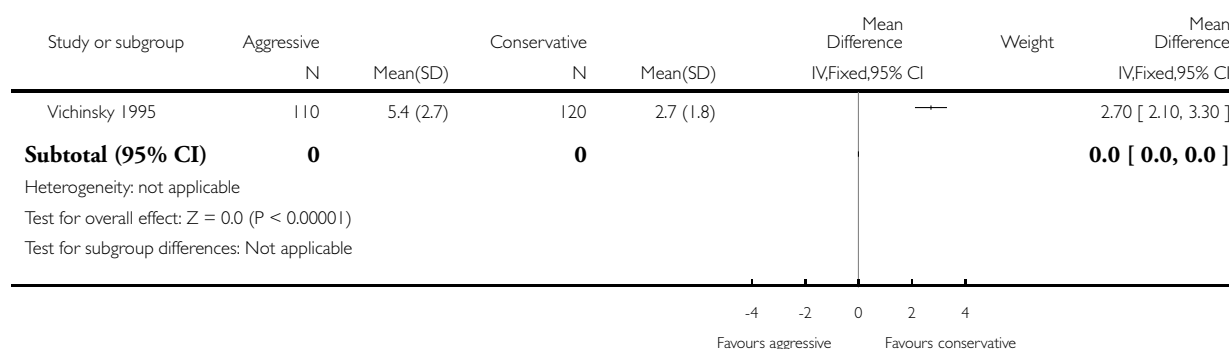


Analysis 1.8. Comparison 1 Aggressive versus conservative blood transfusion, Outcome 8 Cholecystectomy volume of blood transfusion/venesected.

Review: Preoperative blood transfusions for sickle cell disease

Comparison: 1 Aggressive versus conservative blood transfusion

Outcome: 8 Cholecystectomy volume of blood transfusion/venesected

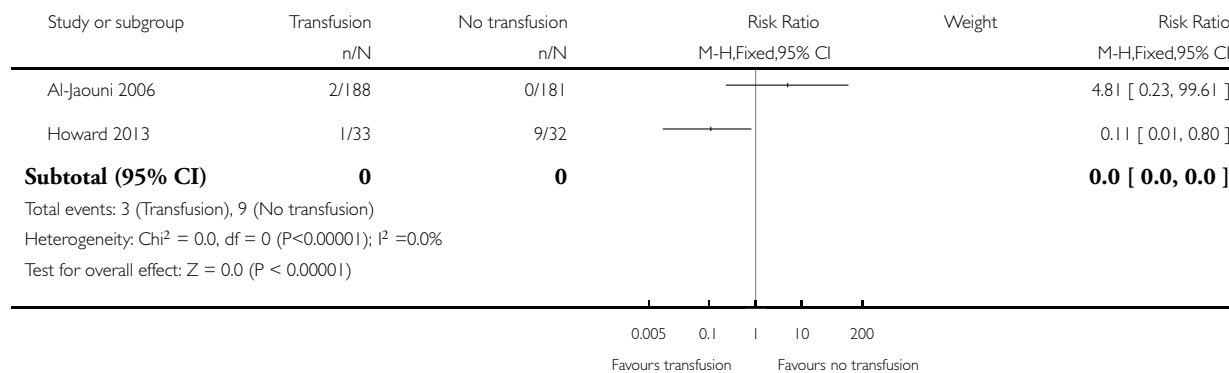


Analysis 2.1. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 1 Serious complications related to sickle cell disease (acute chest syndrome).

Review: Preoperative blood transfusions for sickle cell disease

Comparison: 2 Preoperative blood transfusion versus no transfusion

Outcome: 1 Serious complications related to sickle cell disease (acute chest syndrome)

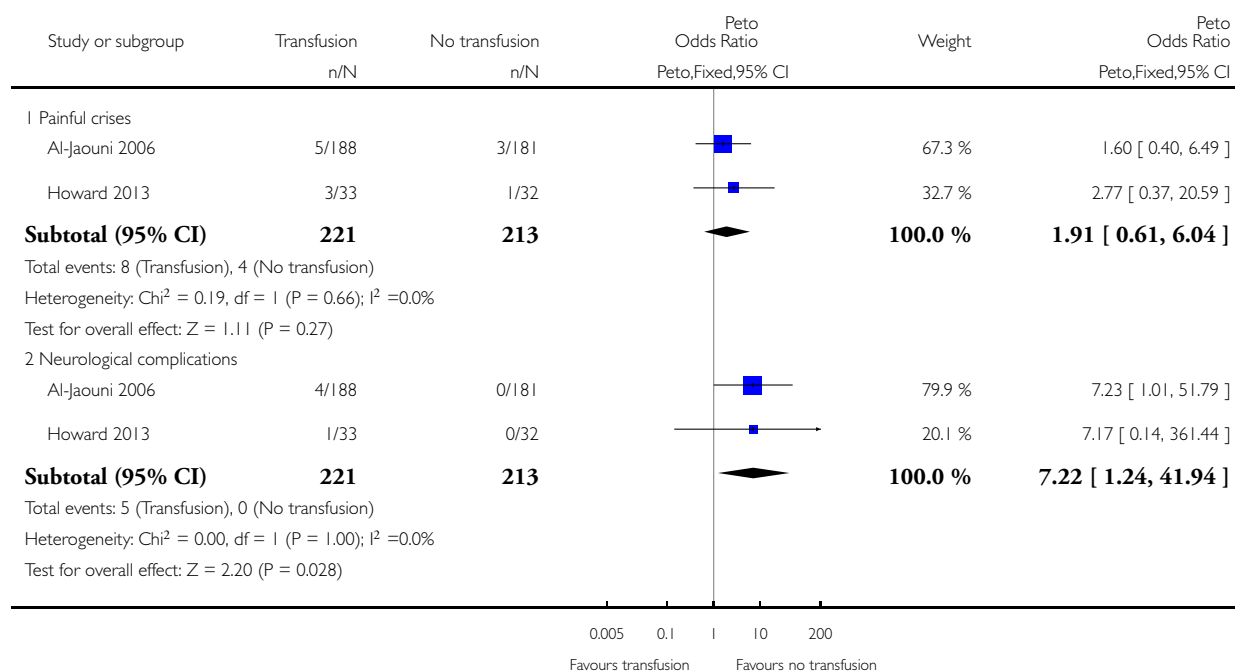


Analysis 2.2. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 2 Serious complications related to sickle cell disease.

Review: Preoperative blood transfusions for sickle cell disease

Comparison: 2 Preoperative blood transfusion versus no transfusion

Outcome: 2 Serious complications related to sickle cell disease

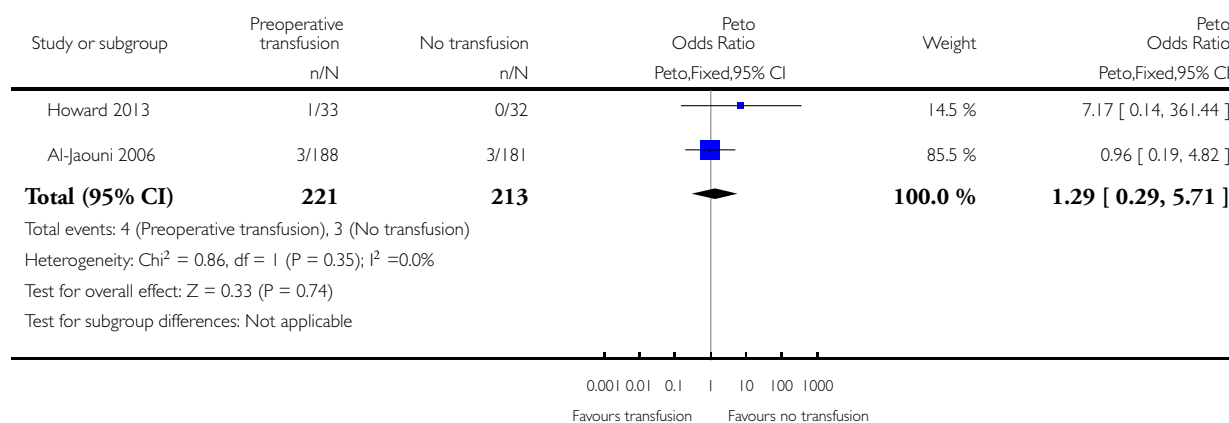


Analysis 2.3. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 3 Serious infection.

Review: Preoperative blood transfusions for sickle cell disease

Comparison: 2 Preoperative blood transfusion versus no transfusion

Outcome: 3 Serious infection

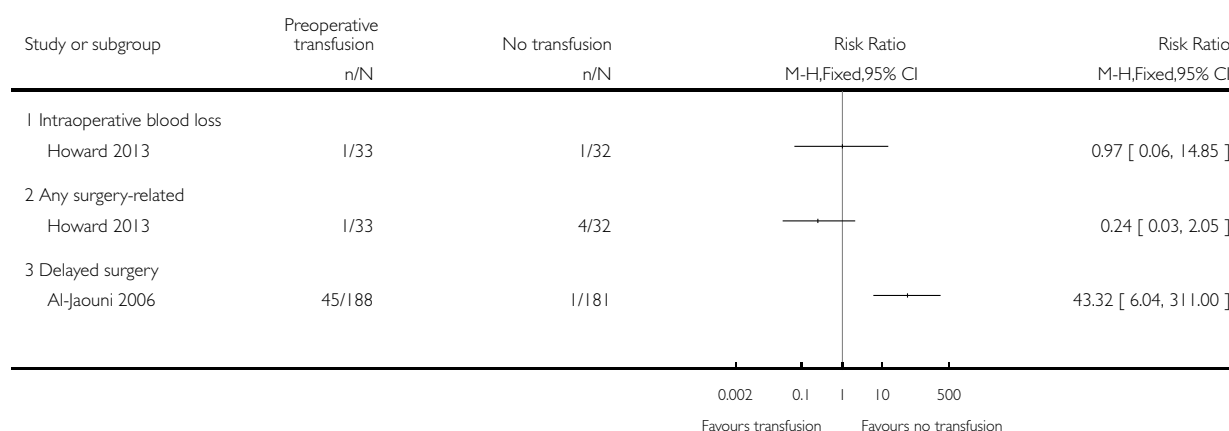


Analysis 2.4. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 4 Perioperative complications.

Review: Preoperative blood transfusions for sickle cell disease

Comparison: 2 Preoperative blood transfusion versus no transfusion

Outcome: 4 Perioperative complications

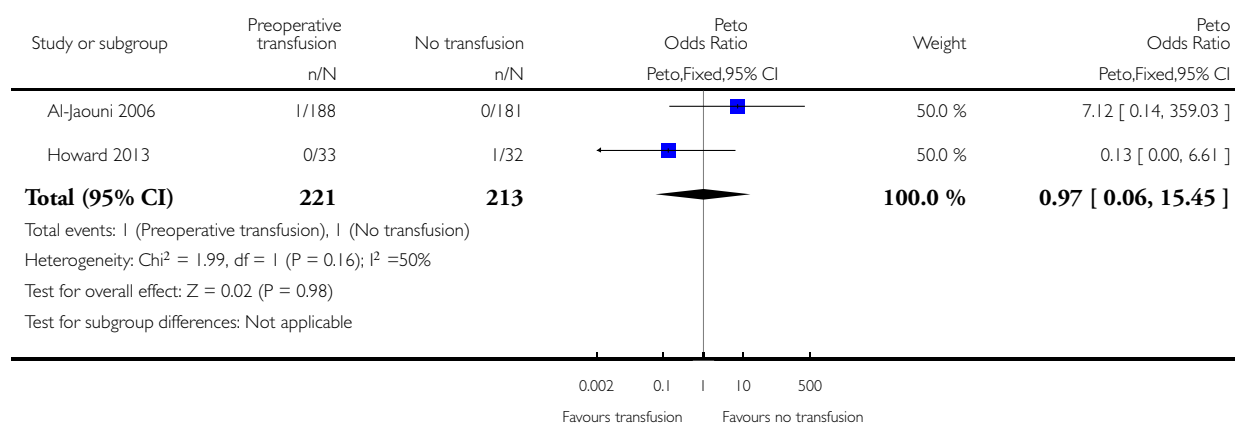


Analysis 2.5. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 5 Perioperative complications (respiratory).

Review: Preoperative blood transfusions for sickle cell disease

Comparison: 2 Preoperative blood transfusion versus no transfusion

Outcome: 5 Perioperative complications (respiratory)

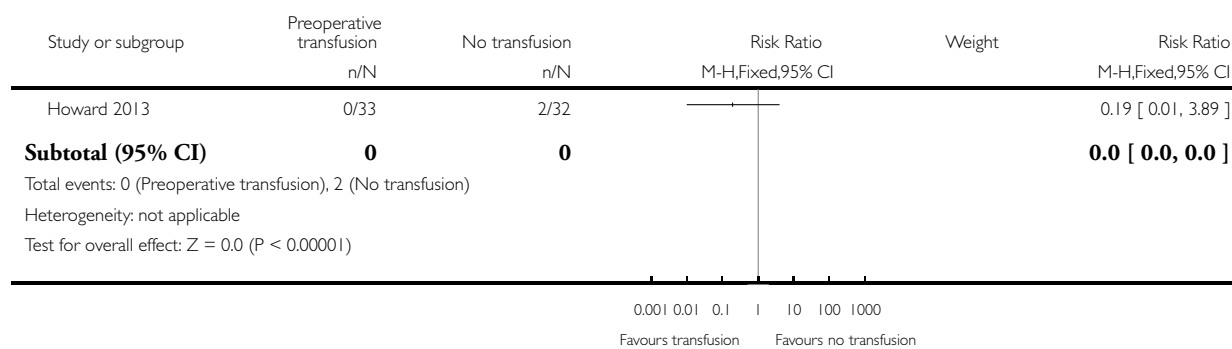


Analysis 2.6. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 6 Postoperative complications (wound complications).

Review: Preoperative blood transfusions for sickle cell disease

Comparison: 2 Preoperative blood transfusion versus no transfusion

Outcome: 6 Postoperative complications (wound complications)

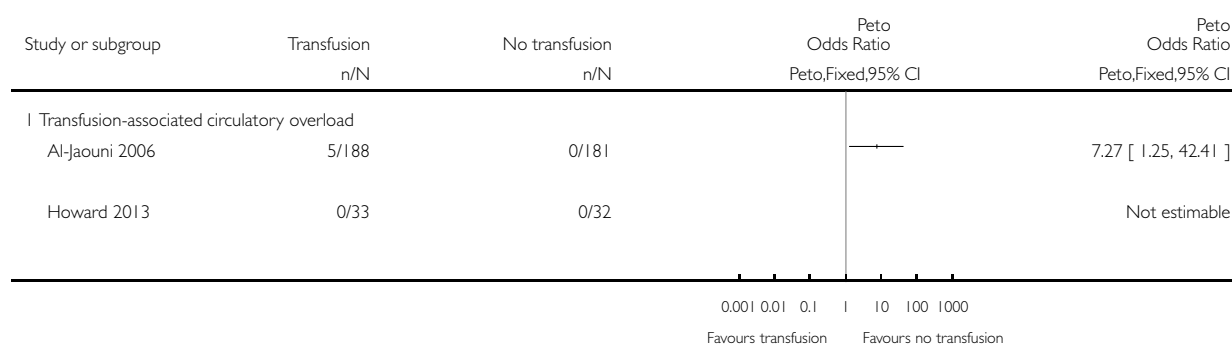


Analysis 2.7. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 7 Transfusion-related complications (serious).

Review: Preoperative blood transfusions for sickle cell disease

Comparison: 2 Preoperative blood transfusion versus no transfusion

Outcome: 7 Transfusion-related complications (serious)

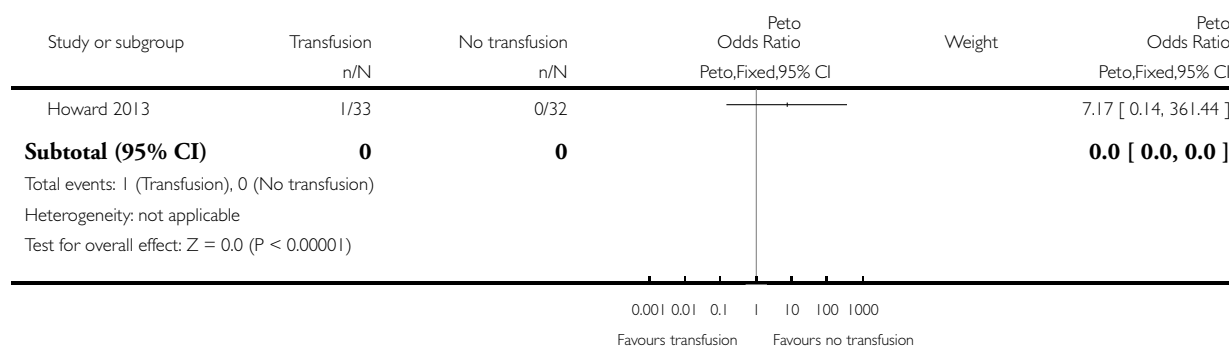


Analysis 2.8. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 8 Transfusion-related complications (new alloantibody).

Review: Preoperative blood transfusions for sickle cell disease

Comparison: 2 Preoperative blood transfusion versus no transfusion

Outcome: 8 Transfusion-related complications (new alloantibody)

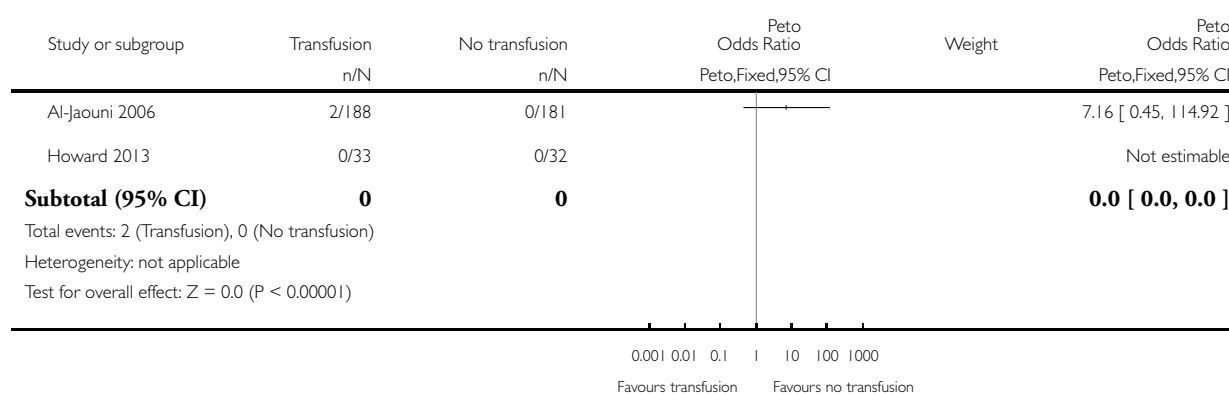


Analysis 2.9. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 9 Transfusion-related complications (transfusion reactions).

Review: Preoperative blood transfusions for sickle cell disease

Comparison: 2 Preoperative blood transfusion versus no transfusion

Outcome: 9 Transfusion-related complications (transfusion reactions)

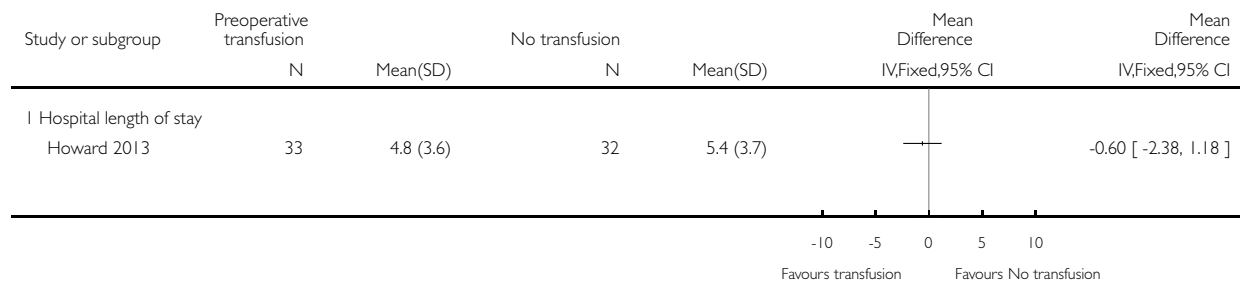


Analysis 2.10. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 10 Length of stay.

Review: Preoperative blood transfusions for sickle cell disease

Comparison: 2 Preoperative blood transfusion versus no transfusion

Outcome: 10 Length of stay

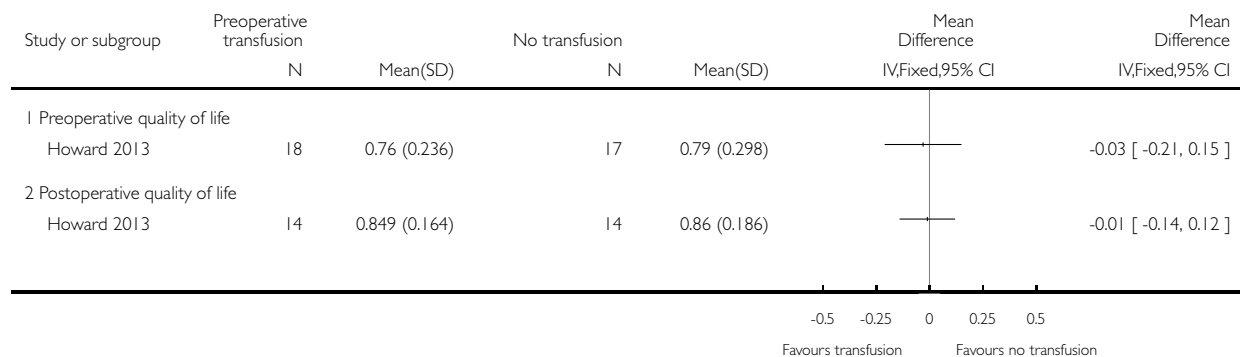


Analysis 2.11. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 11 Quality of life.

Review: Preoperative blood transfusions for sickle cell disease

Comparison: 2 Preoperative blood transfusion versus no transfusion

Outcome: 11 Quality of life

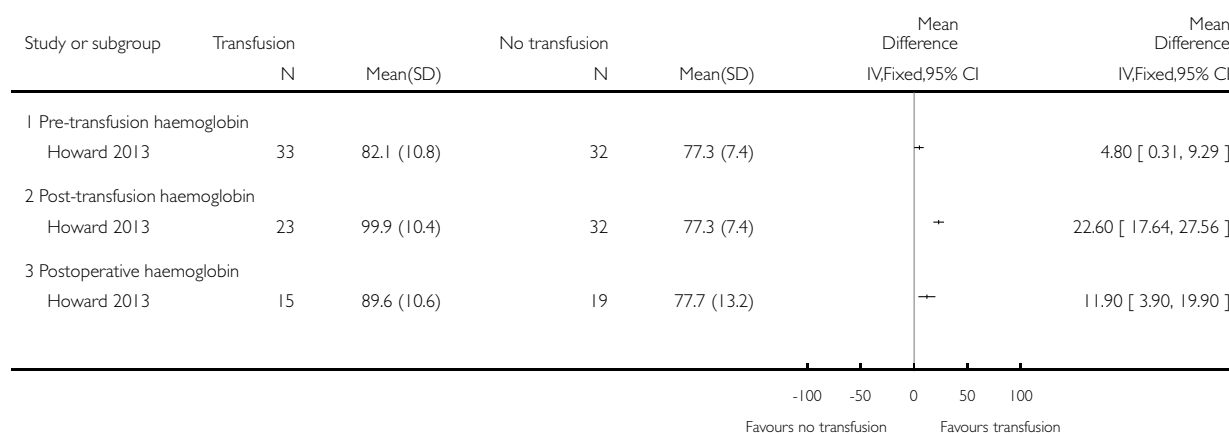


Analysis 2.12. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 12 Haemoglobin concentration.

Review: Preoperative blood transfusions for sickle cell disease

Comparison: 2 Preoperative blood transfusion versus no transfusion

Outcome: 12 Haemoglobin concentration

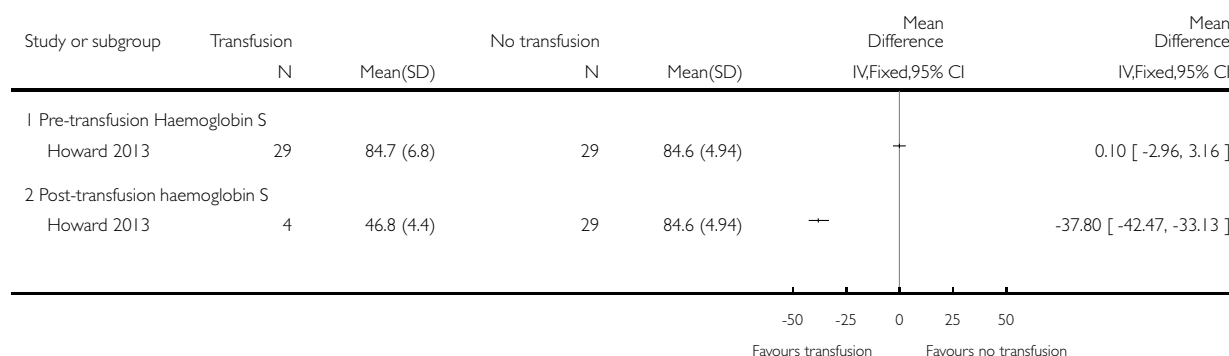


Analysis 2.13. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 13 Haemoglobin S.

Review: Preoperative blood transfusions for sickle cell disease

Comparison: 2 Preoperative blood transfusion versus no transfusion

Outcome: 13 Haemoglobin S

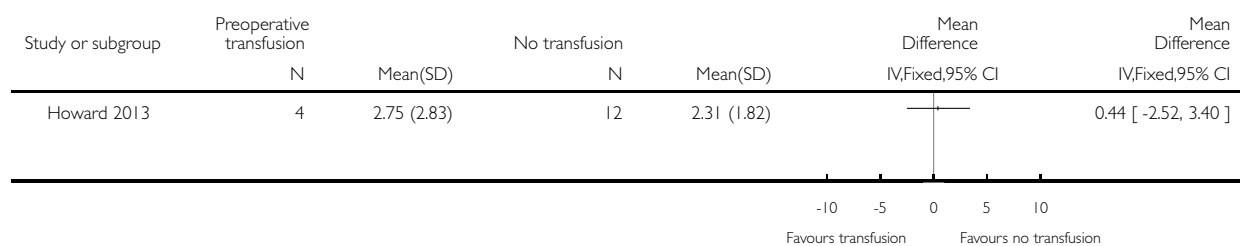


Analysis 2.14. Comparison 2 Preoperative blood transfusion versus no transfusion, Outcome 14 Number of units or volume of red cells transfused.

Review: Preoperative blood transfusions for sickle cell disease

Comparison: 2 Preoperative blood transfusion versus no transfusion

Outcome: 14 Number of units or volume of red cells transfused



APPENDICES

Appendix I. Search Strategies

SEARCH STRATEGIES

THE COCHRANE LIBRARY

#1 MeSH descriptor: [Anemia, Sickle Cell] explode all trees

#2 ("h?emoglobin s" or "h?emoglobin sc" or "h?emoglobin se" or "h?emoglobin ss" or "h?emoglobin c" or "h?emoglobin d" or "Hb s" or "Hb sc" or "Hb se" or "Hb ss" or "Hb c" or "Hb d" or "sc disease*")

#3 ("sickle cell" or sicklemlia or sickled or sickling or meniscocyt* or drepanocyt*)

#4 #1 or #2 or #3

#5 MeSH descriptor: [Blood Transfusion] this term only

#6 MeSH descriptor: [Erythrocyte Transfusion] explode all trees

#7 ((blood or erythrocyte* or "red cell*" or "red blood cell*" or RBC*) near/5 (transfus* or infus* or unit*))

#8 ((red cell* or RBC* or erythrocyte* or red blood cell* or whole blood or transfus*) near/5 (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program* or therapy)):ab

#9 ((red cell* or RBC* or erythrocyte* or blood or transfus*) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)):ti

#10 ("allogeneic blood" or (unit* near/2 blood) or "allogenic blood" or (blood near/2 exposure) or "donor blood" or "blood product*" or "blood component*" or "blood support")

#11 hemotransfus* or haemotransfus* or hypertransfus* or hemotherap* or haemotherap*
 #12 (red cell* or erythrocyte* or blood or RBC*) and transfus*:ti
 #13 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
 #14 MeSH descriptor: [Blood Component Transfusion] this term only
 #15 MeSH descriptor: [Erythrocytes] this term only
 #16 (red cell* or red blood cell* or erythrocyte* or RBC*)
 #17 #14 and (#15 or #16)
 #18 ((transfus* or red cell* or red blood cell* or RBC*) near/10 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practice* or standard*))
 #19 (((transfus* or red cell* or red blood cell* or RBC* or h?ematocrit*) and (level* or critical* or intensive* or h?emorrhag* or bleed*)) or hypertransfus*):ti
 #20 #13 or #17 or #18 or #19
 #21 #4 and #20

MEDLINE (OvidSP)

1. exp Anemia, Sickle Cell/
 2. (h?emoglobin s or h?emoglobin sc or h?emoglobin se or h?emoglobin ss or h?emoglobin c or h?emoglobin d or Hb s or Hb sc or Hb se or Hb ss or Hb c or Hb d or sc disease*).tw.
 3. (sickle cell or sicklemlia or sickled or sickling or meniscocyt* or drepanocyt*).tw.
 4. 1 or 2 or 3
 5. BLOOD TRANSFUSION/
 6. ERYTHROCYTE TRANSFUSION/
 7. ((blood or erythrocyte* or red cell* or red blood cell* or RBC*) adj5 (transfus* or infus* or unit* or therap*)):ti,ab.
 8. ((red cell* or RBC* or erythrocyte* or red blood cell* or whole blood or transfus*) adj5 (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)):ab.
 9. ((red cell* or RBC* or erythrocyte* or blood or transfus*) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)):ti.
 10. (allogeneic blood or (unit* adj2 blood) or allogenic blood or (blood adj2 exposure) or donor blood or blood product* or blood component* or blood support):ti,ab.
 11. (hemotransfus* or haemotransfus* or hypertransfus* or hemotherap* or haemotherap*).tw.
 12. (red cell* or erythrocyte* or blood or RBC*).tw. and transfus*.ti.
 13. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
 14. BLOOD COMPONENT TRANSFUSION/
 15. EXCHANGE TRANSFUSION, WHOLE BLOOD/ or PLASMA EXCHANGE/ or PLATELET TRANSFUSION/ or exp LEUKOCYTE TRANSFUSION/
 16. 14 not 15
 17. ERYTHROCYTES/
 18. (red cell* or red blood cell* or erythrocyte* or RBC*).tw.
 19. 17 or 18
 20. 16 and 19
 21. ((transfus* or red cell* or red blood cell* or RBC*) adj10 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practice* or standard*)):tw.
 22. (((transfus* or red cell* or red blood cell* or RBC* or h?ematocrit*) and (level* or critical* or intensive* or h?emorrhag* or bleed*)) or hypertransfus*):ti.
 23. 13 or 20 or 21 or 22
 24. 4 and 23

Embase (OvidSP)

1. exp Sickle Cell Anemia/
 2. (h?emoglobin s or h?emoglobin sc or h?emoglobin se or h?emoglobin ss or h?emoglobin c or h?emoglobin d or Hb s or Hb sc or Hb se or Hb ss or Hb c or Hb d or sc disease*).tw.
 3. (sickle cell or sicklemlial or sickled or sickling or meniscocyt* or drepanocyt*).tw.
 4. or/1-3
 5. BLOOD TRANSFUSION/
 6. ERYTHROCYTE TRANSFUSION/

7. ((blood or erythrocyte* or red cell* or red blood cell* or RBC*) adj5 (transfus* or infus* or unit* or therap*)).ti,ab.
8. ((red cell* or RBC* or erythrocyte* or red blood cell* or whole blood or transfus*) adj5 (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ab.
9. ((red cell* or RBC* or erythrocyte* or blood or transfus*) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ti.
10. (allogeneic blood or (unit* adj2 blood) or allogenic blood or (blood adj2 exposure) or donor blood or blood product* or blood component* or blood support).ti,ab.
11. (hemotransfus* or haemotransfus* or hypertransfus* or hemotherap* or haemotherap*).tw.
12. (red cell* or erythrocyte* or blood or RBC*).tw. and transfus*.ti.
13. or/5-12
14. BLOOD COMPONENT TRANSFUSION/
15. EXCHANGE TRANSFUSION, WHOLE BLOOD/ or PLASMA EXCHANGE/ or PLATELET TRANSFUSION/ or exp LEUKOCYTE TRANSFUSION/
16. 14 not 15
17. ERYTHROCYTES/
18. (red cell* or red blood cell* or erythrocyte* or RBC*).tw.
19. 17 or 18
20. 16 and 19
21. ((transfus* or red cell* or red blood cell* or RBC*) adj10 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practice* or standard*)).tw.
22. (((transfus* or red cell* or red blood cell* or RBC* or h?ematocrit*) and (level* or critical* or intensive* or h?emorrhag* or bleed*)) or hypertransfus*).ti.
23. 13 or 20 or 21 or 22
24. 4 and 23

PubMed (epublications (publications ahead of print) only)

- #1 ("hemoglobin s" OR "haemoglobin s" OR "hemoglobin sc" OR "haemoglobin sc" OR "hemoglobin se" OR "haemoglobin se" OR "hemoglobin ss" OR "haemoglobin ss" OR "hemoglobin c" OR "haemoglobin c" OR "hemoglobin d" OR "haemoglobin d" OR "Hb s" OR "Hb sc" OR "Hb se" OR "Hb ss" OR "Hb c" OR "Hb d" OR "sc disease*")
- #2 ("sickle cell*" OR sicklemlia OR sickled OR sickling OR meniscocyt* OR drepanocyt*)
- #3 #1 OR #2
- #4 ((blood OR erythrocyte* OR "red cell*" OR "red blood cell*" OR RBC*) AND (transfus* OR infus* OR unit*))
- #5 ((red cell* OR RBC* OR erythrocyte* OR red blood cell* OR whole blood OR transfus*) AND (use* OR usage* OR utiliz* OR utilis* OR requir* OR need* OR administ* OR replac* OR support* OR strateg* OR management OR practic* OR indicat* OR criteri* OR standard* OR program* OR therapy))
- #6 ("allogeneic blood" OR "unit* of blood" OR "allogenic blood" OR "blood exposure" OR "donor blood" OR "blood product*" OR "blood component*" OR "blood support")
- #7 hemotransfus* OR haemotransfus* OR hypertransfus* OR hemotherap* OR haemotherap*
- #8 (red cell* OR erythrocyte* OR blood OR RBC*) and transfus*[TI]
- #9 ((transfus* OR red cell* OR red blood cell* OR RBC*) AND (trigger* OR threshold* OR target* OR restrict* OR liberal* OR aggressive* OR conservative* OR prophylactic* OR limit* OR protocol* OR policy OR policies OR practice* OR standard*))
- #10 #4 OR #5 OR #6 OR #7 OR #8 OR #9
- #11 #3 AND #10
- #12 (random* OR blind* OR control group OR placebo OR controlled trial OR controlled study OR groups OR trials OR systematic review OR meta-analysis OR metaanalysis OR literature search OR medline OR cochrane OR embase) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])
- #13 #11 AND #12

ClinicalTrials.gov & ICTRP

Conditions: sickle cell disease

Interventions: transfusion

WHAT'S NEW

Last assessed as up-to-date: 23 March 2016.

Date	Event	Description
23 March 2016	New search has been performed	One new completed trial has been included in this updated version of the review (Howard 2013). Nine further studies have been added to the 'Excluded studies' section (Alotaibi 2014 ; Aziz 2011 ; Daigavane 2013 ; Debaun 2007 ; El-Shafei 1995 ; Geoghegan 2015 ; Koshy 1988 ; Orringer 1995 ; Styles 2007).
23 March 2016	New citation required and conclusions have changed	A new review team has produced this updated version of the review which now conforms to the current Cochrane standards. This is a major update and the conclusions have been amended. A third trial (70 participants) has now been included in the review (Howard 2013).

HISTORY

Protocol first published: Issue 3, 2001

Review first published: Issue 3, 2001

Date	Event	Description
1 December 2011	New citation required but conclusions have not changed	Minor update. No new information has been added to the review
11 November 2011	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register did not identify any potentially eligible trials for inclusion in this update of the review
15 December 2009	New search has been performed	A search of the Group's Trials Register identified the full published paper to an already included abstract (Al-Jaouni 2006).
1 October 2008	Amended	Converted to new review format.
1 August 2007	New search has been performed	The search of the Haemoglobinopathies Trials Register identified no new trials eligible for inclusion in this review
1 August 2007	Amended	The 'Synopsis' has been replaced by a 'Plain language summary'

(Continued)

1 August 2006	New search has been performed	The search of the Haemoglobinopathies Trials Register identified no new trials eligible for inclusion in this review
1 April 2005	New search has been performed	The search of the Haemoglobinopathies Trials Register identified no new trials eligible for inclusion in the review The lead author has changed her family name from Riddington to Hirst
1 March 2004	New search has been performed	The searches found two new trials. One trial was eligible for inclusion (Al-Jaouni 2002), but the other was ineligible, as it did not use a randomised design (Wali 2003) The new data from the Al-Jaouni trial demonstrated no advantage in using preoperative blood transfusion in 369 people with sickle cell disease undergoing surgery in Saudi Arabia. There was no significant reduction in sickle related events in the preoperative transfusion group, and an increase in transfusion related complications
3 March 2003	New search has been performed	The searches found no new trials eligible for inclusion.
1 February 2002	New search has been performed	No further data to add, no substantive update.

CONTRIBUTIONS OF AUTHORS

- Lise Estcourt: searching; selection of trials; eligibility and methodological quality assessment; data extraction and analysis; and content expert.
- Carolyn Doree: searching; selection of trials; and final report.
- Patricia Fortin: searching; selection of trials; eligibility and methodological quality assessment; data extraction and analysis.
- Sally Hopwell: methodological expert.
- Marialena Trivella: methodological expert.

DECLARATIONS OF INTEREST

- Lise Estcourt is partly funded by an NIHR Cochrane Programme Grant.
- Carolyn Doree: none to declare.
- Patricia Fortin is funded by an NIHR Cochrane Programme Grant.
- Sally Hopwell is partly funded by an NIHR Programme Grant
- Marialena Trivella is partly funded by an NIHR Programme Grant

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To provide funding for systematic reviewers and methodological support from the Centre for Statistics in Medicine, Oxford

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Changes from previous versions of the review:

Since the protocol for the review was not available we report on changes in this current version of the review from previous versions of the review ([Hirst 2001](#); [Hirst 2012](#)).

Objectives

We have added an additional objective. “To compare the effectiveness of different transfusion regimens (aggressive or conservative) if preoperative transfusions are indicated in patients with sickle cell disease.” This was implicit in the previous review but not explicitly stated.

Types of outcome measures

We amalgamated four outcomes for serious complications

1. Serious complications related to:
 - i) sickle cell disease (e.g. acute chest syndrome, painful crisis, neurological complication, renal complication);
 - ii) surgery (e.g. fall in haemoglobin level);
 - iii) infection;
 - iv) transfusion (e.g. serious transfusion reactions, other serious transfusion complications).

We also made some minor rewording changes to the primary outcome of perioperative mortality by adding all-cause, For the secondary outcome for quality of life we added as measured on a validated scale.

Unit of analysis issues

Unit of analysis issues were not identified in the previous versions of this review. There were unit of analysis issues with [Vichinsky 1995](#). We did not report the data in the Vichinsky primary publication on all 551 participants (with 604 procedures), as we could not obtain patient specific data excluding the patients who were re-randomised. We therefore used subsets of the data from two

publications reporting on cholecystectomy patients (230 participants) ([Haber Kern 1997](#)) and tonsillectomy or adenoidectomy patients (107 participants) ([Waldron 1999](#)) where we knew patients could only be randomised once.

Data synthesis

We changed from reporting the odds ratio to reporting the Mantel-Haenszel risk ratio method for dichotomous outcomes because its interpretation is more familiar to patients and health professionals. Where appropriate, we used the Peto odds ratio when fewer than 5% of participants experienced an outcome.

Summary of findings

We used the GRADE approach to build a 'Summary of Findings' table as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Schünemann 2011](#)). We used the GRADE approach to rate the quality of the evidence as 'high', 'moderate', 'low', or 'very low' using the five GRADE considerations. This had not been done in the previous versions of the review.

Characteristics of included studies and risk of bias tables

We added more information on the included trials, and added baseline characteristics of participants and more details on methods and interventions. We also added 'blinding of outcome assessment', 'selective reporting' and 'other bias' to the risk of bias assessment.

Study flow diagram

We created a study flow diagram and based it on guidance adapted from the PRISMA flow diagram and recommended for updates to Cochrane reviews ([Stovold 2014](#)).

Aspects of the review that were not implemented due to lack of data

Publication bias: we did not perform a formal assessment of potential publication bias (small trial bias) because there were fewer than 10 trials within this review ([Sterne 2011](#)).

Outcomes: we were unable to group outcome data, with the exception of transfusion-related complications, into those measured during surgery and at three hours, 24 hours, one week and one month after surgery.

Subgroup analyses: due to lack of data, two of the three pre-specified sub-group analyses was not performed, these were severity of the disease and age of the patient.

Meta-regression was not performed because no subgroup contained more than 10 trials ([Deeks 2011](#)). Differences between subgroups were commented on as a narrative.

Assessment of heterogeneity between trials due to age of trial or type of transfusion was not performed due to lack of data.

Sensitivity analyses: we planned to use the random-effects model for sensitivity analyses as part of the exploration of heterogeneity. We could not do sensitivity analyses due to inadequate data.

INDEX TERMS

Medical Subject Headings (MeSH)

*Hemoglobin, Sickle; Anemia, Sickle Cell [blood; *surgery]; Blood Transfusion [adverse effects; *methods]; Preoperative Care [*methods]; Randomized Controlled Trials as Topic

MeSH check words

Humans