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[Intervention Review]

Blood transfusions for treating acute chest syndrome in people with sickle cell disease

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ABSTRACT

Background

Sickle cell disease is an inherited autosomal recessive blood condition and is one of the most prevalent genetic blood diseases worldwide. Acute chest syndrome is a frequent complication of sickle cell disease, as well as a major cause of morbidity and the greatest single cause of mortality in children with sickle cell disease. Standard treatment may include intravenous hydration, oxygen as treatment for hypoxia, antibiotics to treat the infectious cause and blood transfusions may be given. This is an update of a Cochrane Review first published in 2010 and updated in 2016.

Objectives

To assess the effectiveness of blood transfusions, simple and exchange, for treating acute chest syndrome by comparing improvement in symptoms and clinical outcomes against standard care.

Search methods

We searched The Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register, which comprises references identified from comprehensive electronic database searches and handsearching of relevant journals and abstract books of conference proceedings.

Date of the most recent search: 30 May 2019.

Selection criteria

Randomised controlled trials and quasi-randomised controlled trials comparing either simple or exchange transfusion versus standard care (no transfusion) in people with sickle cell disease suffering from acute chest syndrome.

Data collection and analysis

Both authors independently selected trials and assessed the risk of bias, no data could be extracted.

Main results

One trial was eligible for inclusion in the review. While in the multicentre trial 237 people were enrolled (169 SCC, 42 SC, 15 S β^0 -thalassaemia, 11S β^+ -thalassaemia); the majority were recruited to an observational arm and only ten participants met the inclusion criteria for randomisation. Of these, four were randomised to the transfusion arm and received a single transfusion of 7 to 13 mL/kg packed red blood cells, and six were randomised to standard care. None of the four participants who received packed red blood cells developed

acute chest syndrome, while 33% (two participants) developed acute chest syndrome in standard care arm. No data for any pre-defined outcomes were available.

Authors' conclusions

We found only one very small randomised controlled trial; this is not enough to make any reliable conclusion to support the use of blood transfusion. Whilst there appears to be some indication that chronic blood transfusion may play a roll in reducing the incidence of acute chest syndrome in people with sickle cell disease and albeit offering transfusions may be a widely accepted clinical practice, there is currently no reliable evidence to support or refute the perceived benefits of these as treatment options; very limited information about any of the potential harms associated with these interventions or indeed guidance that can be used to aid clinical decision making. Clinicians should therefore base any treatment decisions on a combination of; their clinical experience, individual circumstances and the unique characteristics and preferences of adequately informed people with sickle cell disease who are suffering with acute chest syndrome. This review highlights the need of further high quality research to provide reliable evidence for the effectiveness of these interventions for the relief of the symptoms of acute chest syndrome in people with sickle cell disease.

PLAIN LANGUAGE SUMMARY

Blood transfusions for treating acute chest syndrome in people with sickle cell disease

Review question

We reviewed the effectiveness of blood transfusions, for treating acute chest syndrome by comparing improvement in symptoms and clinical outcomes against standard care. This is an update of a Cochrane Review first published in 2010 and updated in 2016.

Background

Sickle cell disease (SCD) is an inherited blood condition affecting over 250 million people worldwide and is particularly common in Sub-Saharan Africa, South and Central America, Saudi Arabia, India and a number of Mediterranean countries. It is characterized by the presence of sickle-shaped red blood cells which are capable of blocking the blood vessels causing pain and severe damage to several organs of the body. People with SCD may have the acute onset of chest problems which may include fever, this is called acute chest syndrome. Treatment will depend on the individuals' clinical condition and the severity of the symptoms. Standard treatment consists of supportive care, antibiotics, intravenous fluids and blood transfusion, either simple or exchange, may also be indicated.

Search date

The evidence is current to: 30 May 2019.

Key results

One study was included in the review, there were two parts to the study, one larger observational study and one randomised trial which was to assess transfusion versus standard care to prevent acute chest syndrome in people with sickle cell disease, while twenty-six centres were contracted. Only 10 participants were enrolled into the randomised trial. The effects of blood transfusions could not be determined from the trial; there were no data that could be presented or therefore analysed within this review for the very small number of participants enrolled.

Therefore, this unique study did not show how effective blood transfusions might be for treating acute chest syndrome in people with sickle cell disease. Future research is needed to provide evidence for people to make informed decisions on whether blood transfusions are effective for treating acute chest syndrome in people with sickle cell disease.

BACKGROUND

Description of the condition

Aetiology and prevalence

Sickle cell disease (SCD) is an inherited autosomal recessive blood condition in which either both sickle haemoglobin genes or one sickle haemoglobin gene with another gene of an abnormal haemoglobin, e.g. thalassaemia gene have been inherited. It is one of the most prevalent genetic blood diseases worldwide. It is particularly common in Sub-Saharan Africa, South and Central America, Saudi Arabia, India and a number of Mediterranean countries (Alvim 2005; El-Hazmi 1998; Fleming 1989; Loureiro 2005). Annually, worldwide, there are approximately over 300,000 SCD-affected conceptions or births (Piel 2012).

Abnormal haemoglobin genes inherited from both parents are responsible for several different forms of the disease. The most commonly seen types of SCD include homozygous sickle cell (SS), a disease in which the sickle haemoglobin (HbS) gene is inherited from both parents; sickle cell-haemoglobin C (SC) disease in which the genes for HbS and HbC are inherited; and two further types resulting from the interaction of HbS genes with those for beta thalassaemia; sickle cell/ β^0 -thalassaemia and sickle cell/ β^+ -thalassaemia ($S\beta^0$ and $S\beta^+$). Homozygous sickle cell (SS) disease and sickle cell/ β^0 -thalassaemia are generally considered the more severe forms of the disease whilst SC disease and sickle cell/ β^+ -thalassaemia tend to be milder.

The main clinical features result from the tendency of HbS molecules to polymerise, leading to a reduced pliability of the red blood cells which are then prematurely broken down and eventually cause blockages and reduced flow in some of the blood vessels (vaso-occlusion). Chronic haemolytic anaemia, increased susceptibility to infections, recurrent episodes of pain, an increased risk of stroke and multiple organ dysfunction are some of the potentially serious complications in SCD (Njamnshi 2006; Serjeant 1995).

Acute chest syndrome (ACS) is a frequent complication of SCD, as well as a major cause of morbidity and the greatest single cause of mortality in SCD from the age of two years (Vichinsky 2000). An infectious agent is identified in more than one third of the cases, however, because of the life-threatening nature of the syndrome, broad antibiotic therapy is usually administered, even if infection was not the clear etiology. Hypoxemia in ACS is postulated to be due to sickling in the pulmonary vasculature which results in a ventilation and perfusion mismatch (Emre 1995).

Data from the Clinical Course of Sickle Cell Disease Cooperative Study indicate that ACS occurs with a rate of 10.5 per 100 patients per year (Castro 1994).

Symptoms and diagnosis

Acute chest syndrome has been defined as a new infiltrate visible on chest radiograph associated with one or more symptoms, such as fever, cough, sputum production, tachypnoea, dyspnoea (breathing difficulties), or new-onset hypoxia (poor oxygenation) (Vichinsky 2000). Complications occurring in the lungs include infection and infarction (death of tissue due to blockage of the blood vessels by blood clots or bone marrow fat), and whilst infection occurs predominately in children and infarction

more commonly in adults, these two are often interrelated and may occur concurrently (Taylor 2004). Rates of infection have been reported as: chlamydia 7.2%; mycoplasma 6.6%; viruses 6.4%; and *Streptococcus pneumoniae*, 4.3% (Vichinsky 2000). A further complication is the acute fragmentation of red blood cells (haemolysis) in the pulmonary vessels. Recurrent attacks of ACS may also result in pulmonary fibrosis, pulmonary hypertension, and right-sided heart failure.

Symptoms and complications of ACS may vary quite widely between people with SCD. The severity of the clinical manifestations varies from one person to another according to the general health state, age and the etiology of a particular episode of ACS. Some individuals face a higher risk of mortality, while others have a longer life expectancy once they receive good medical care (Golden 1998; Vichinsky 1997). The treatment strategies will therefore need to be modified and different decisions needed to be made by individual patient status.

Description of the intervention

Management of ACS depends on the individuals' clinical condition and presenting complaint. Standard treatment is intravenous hydration to maintain the individuals' euvolemic especially in the presence of dehydration, oxygen as treatment for hypoxia and antibiotics to treat the infectious cause and often blood transfusion (Emre 1995). Other treatment modalities include vasodilation, anticoagulation, inhaled nitrous oxide (Al Hajeri 2008), antibiotics (Martí-Carvajal 2019) and inhaled bronchodilators (Knight-Madden 2016). Dexamethasone was previously also used as an alternative treatment (Bernini 1998); but a recent study has shown an increased duration of admission and risk of re-admission in children treated with dexamethasone for ACS, so this is no longer recommended (Strouse 2009). In SCD, transfusion may prevent complications (Emre 1995). There are two modalities of red cell transfusion, simple and exchange transfusion. The vast majority of transfusions for SCD are simple red cell transfusions, which are useful when added oxygen capacity is needed and in conditions where the haemoglobin has dropped to a level significantly below the steady state (Swerdlow 2006). Red cell exchange transfusion is an effective but perhaps under-utilised treatment for both acute and chronic complications of SCD. It is given in severe or rapidly progressive illness, when the individuals Hb is 10 gm or more and the HbS is greater than 30%. Recently a review article published by Farooq emphasized the indication of chronic transfusion therapy in recurrent episodes of moderate-to-severe ACS in sickle cell crises, to maintain the haemoglobin S percentage below 50% (Farooq 2018). This idea has been evidenced previously in the Stroke Prevention Trial (STOP) trial, which showed that chronic transfusion therapy decreased the incidence of ACS, and prevented secondary stroke in sickle cell crises (STOP 1998).

How the intervention might work

Simple red cell transfusions consist of packed red cells administered intravenously. Hemoglobin concentration and blood viscosity is noted to increase after simple transfusions unless there is rapid cell destruction or bleeding (Gladwin 1999). Simple blood transfusion is given if there is a moderate to severe illness and the haemoglobin is greater than 1 mg/dL below baseline.

The goal of exchange transfusion is to remove the sickled cells (HbS) and replace them with adult haemoglobin (HbA) which also

contributes to reducing the blood viscosity (Vichinsky 2000). In a red cell exchange, the individuals red cells are removed and replaced by exogenous normal red cells. The exchange prevents the removed sickle cells from participating in new vaso-occlusive events, reduces haemolytic complications, and provides added oxygen carrying capacity while decreasing the blood viscosity. It is given in severe or rapidly progressive illness, when the individuals Hb is 10 gm or more and the HbS is greater than 30%.

Why it is important to do this review

Clinical standards and guidelines in the UK and USA strongly recommend the exchange transfusion method for treating symptomatic severe acute chest syndrome in people with SCD (Yawn 2014), but the quality of evidence in this area is still low, with a very small number of RCTs looking at the routine management of ACS (Yawn 2014). A systematic review is needed to identify and assess the evidence, and to then impact on new research programs for the use of blood transfusions for treating acute chest syndrome in people with SCD. This is an update of a Cochrane Review first published in 2010 and updated in 2016.

OBJECTIVES

To assess the effectiveness of blood transfusions, simple and exchange, for treating ACS by comparing improvement in symptoms and clinical outcomes against standard care.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-randomised trials.

Types of participants

People with SCD: SS; SC; S β ⁰; S β ; S β + (confirmed by electrophoresis and sickle solubility test, with family studies or DNA tests as appropriate) of all ages and both sexes with ACS, in any setting.

The definition of ACS was according to the clinical signs, symptoms and criteria described by Vichinsky as; a new infiltrate visible on chest radiograph associated with one or more symptoms, such as fever, cough, sputum production, tachypnoea, dyspnoea, or new-onset hypoxia (Vichinsky 2000).

Types of interventions

Simple and red cell exchange transfusions during the ACS period, would be considered separately:

1. simple transfusion versus standard care (no transfusion);
2. exchange transfusion versus standard care (no transfusion).

Types of outcome measures

Primary outcomes

1. Chest pain
 - a. intensity (expressed as scores obtained through any validated patient-reported outcomes instrument either generic or SCD specific)
 - b. duration from time of start of symptoms

2. Fever
3. Mortality

Secondary outcomes

1. Duration of any assisted ventilation
2. Duration of hospitalisation in the intensive care unit (ICU) (number of inpatient days)
3. Mean duration of opioid therapy
4. Laboratory investigations:
 - a. concentration of haemoglobin S
 - b. pulmonary function tests
 - c. pulse oximetry to diagnose hypoxia
5. Quality of life (e.g. absence from school, lost time at work, mobility) as assessed by any validated questionnaire either generic or SCD specific
6. Participant satisfaction with the intervention assessed by any appropriate and validated questionnaire (either generic or SCD specific)

Adverse effects

We intended reporting on any specific adverse effects, systemic or local, toxicity, any clinically diagnosed hypersensitivity or other unacceptable or adverse events associated with this intervention.

Search methods for identification of studies

Electronic searches

We conducted searches in the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register using the terms: sickle cell AND acute chest syndrome.

The Haemoglobinopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (Clinical Trials) (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 Public Health Agency Annual Scientific Meeting (formerly the Caribbean Health Research Council Meeting); 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 Cochrane Cystic Fibrosis and Genetic Disorders Group's [website](#).

Date of the last search: 30 May 2019.

We also searched the ClinicalTrials.gov database (www.ClinicalTrials.gov) and the WHO ICTRP database (www.who.int/ictrp/search/en/) in an effort to identify any additional relevant clinical studies and registered clinical trials of the same topic. Regarding the relatively high prevalence of hereditary SCD (SS) and others associated disorders in south provinces of Iran (Zandian 2012), we tried to find any additional RCT studies registered in Iranian Registry of Clinical Trials (www.irct.ir).

Searching other resources

We contacted the trial authors of the PROACTIVE trial for further data and information, but to date have received no response (PROACTIVE 2012).

For future updates, if further trials become available we will attempt to contact investigators of these trials by either conventional or electronic mail to ask for details of additional published and unpublished trials. The reference lists of any clinical trials identified will be cross checked and the review authors' personal databases examined in an attempt to identify any other relevant trials.

There would have been no language restrictions on included trials and if necessary the authors would have arranged to translate and report any relevant non-English papers.

Data collection and analysis

Selection of studies

Two authors independently assessed the abstracts of trials identified from the searches. We obtained full copies of all potentially relevant trials, i.e. those appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision. The two review authors independently assessed the full text papers independently and resolved any disagreement on their eligibility for this review through discussion and consensus; or if necessary through a third party (an editor from the Cochrane Cystic Fibrosis and Genetic Disorders Group). After assessment, the authors eliminated from further review any remaining trials that did not match the inclusion criteria and noted the reasons for their exclusion in the 'Characteristics of excluded studies' table.

Data extraction and management

The following methods of data extraction, assessment of risk of bias and data management will apply for subsequent updates, if any further trials are identified.

Data will be collected using a predetermined form designed for this purpose. Trial details will be entered into the 'Characteristics of included studies' table and extracted data will be entered separately by each of two review authors into the 'Data and analyses' table in Review Manager 5 and automatically checked for differences (RevMan 2014). We will only include data if there is an independently reached consensus and any disagreements will be discussed and if required a third review author will be consulted.

The following details will be extracted.

1. Trial methods: method of allocation; masking of participants; exclusion of participants after randomisation; and proportion of and reasons for follow-up losses.
2. Participants: country of origin; sample size; age; sex; inclusion and exclusion criteria as described in the [Criteria for considering studies for this review](#).
3. Intervention: type; frequency; and duration of usage.
4. Control: type; dose and frequency of any comparison or placebo.
5. Outcomes: primary and secondary outcomes as described in the outcome measures section of this protocol.

If stated, the sources of funding of any of the included trials will be recorded.

This information will be used to help assess heterogeneity and the external validity of the trials.

We will focus on outcomes assessments at the following time points: 24 hours, 48 to 72 hours and one month post intervention. Data, if available, will be grouped accordingly prior to analysis. If data are reported at other time periods, consideration will be given to examining these as well.

Assessment of risk of bias in included studies

For future updates, when more trials are included, both review author will assess every trial using a simple form and will follow the domain-based evaluation as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The assessments will be compared and any inconsistencies between the review authors in the interpretation of inclusion criteria and their significance to the selected trials will be discussed and resolved.

Each trial will be assessed as having either a low, unclear or high risk of bias in relation to the following domains.

1. Randomisation

Those assessed as having a low risk of bias in this domain will include, e.g. methods such as: computer generated or table of random numbers, drawing of lots, coin-toss, shuffling cards or throw of a dice. We will assess those as having an unclear risk of bias, where trials are reported as being randomised, but where no description of the methods used to allocate participants to treatment group was described. We will judge trials as having a high risk of bias where methods of randomisation such as use of case record number, date of birth, or alternate numbers are used.

2. Concealment of allocation

Those assessed as having a low risk of bias in this domain will include, e.g. those who have used of a central independent randomisation unit or sequentially numbered sealed opaque envelopes. We will assess as unclear those trials where the method used to conceal the allocation was either not described, or not described in sufficient detail to enable a judgement to be made. We will judge trials to have a high risk of bias in this domain if there was an open allocation sequence and the participants and trial investigators could potentially foresee the upcoming assignment.

3. Blinding (of participants, personnel and outcome assessors)

Those assessed as having a low risk of bias in this domain will include no blinding (where a judgement is made that the outcome and outcome assessment are not likely to be influenced by lack of blinding) and blinding of participants and key trial personnel ensured, and unlikely that blinding could have been broken. We will assess trials as unclear where there is insufficient information to permit judgement of low or high risk or where the trial did not address the outcome. We will judge trials as having a high risk of bias in this domain, e.g. where there has been no blinding or incomplete blinding, and the outcome assessment is likely to be influenced by this; or where blinding of key trial participants and personnel attempted, but likely that it was broken.

4. Incomplete outcome data

Those assessed as having a low risk of bias in this domain will include those where there was no missing outcome data; missing outcome data balanced in numbers across groups, with similar reasons for missing data across groups; and reasons for missing

data unlikely to be related to true outcome. We will assess as unclear those trials where this outcome was not addressed and where there was insufficient reporting of attrition or exclusions, or both, to permit judgement of low or high risk. We will judge as high risk, e.g. those trials where reasons for missing data are likely to be related to the true outcome, with, e.g. imbalance in numbers or where 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.

5. Selective outcome reporting

Those assessed as having a low risk of bias in this domain will include, e.g. where the trial protocol is available and where all the pre-specified outcomes have been reported in the pre-specified way. We will assess as unclear those trials where there is insufficient information to permit judgement of low or high risk. We will judge as high risk, e.g. those trials where not all of the trial's pre-specified primary outcomes have been reported; and where one or more reported primary outcomes were not pre-specified (unless clear justification provided).

Measures of treatment effect

There were no data available for the included trial. For future updates of this review, when new trials are included, we will seek advice from the Cochrane Cystic Fibrosis and Genetic Diseases Group with regards to statistical analysis for data synthesis. To analyse the data we will use Review Manager 5 and report the results according to Cochrane criteria ([RevMan 2014](#)). We plan to analyse binary data and report the risk ratio with corresponding 95% confidence intervals; we will analyse continuous outcomes and report mean differences between treatment groups and their 95% confidence intervals.

Results of clinically homogeneous trials will be pooled to provide estimates of the efficacy of the interventions only if the included trials have similar interventions received by similar participants. Number needed to treat to benefit (NNTB) and number needed to treat to harm (NNTH) will be calculated for the whole pooled estimates with 95% confidence intervals.

Unit of analysis issues

For future updates of this review, should data be available for included trials, where trials measure data longitudinally, we plan to base the analysis on the final time-point results. Methods are not yet available to carry out a meta-analysis of aggregate longitudinal data, where individual patient data (IPD) are not available ([Jones 2009](#)).

If we are able to combine results from crossover trials we plan to use the methods recommended by Elbourne ([Elbourne 2002](#)). However, if only limited data are available, we will only be able to either use the first-arm data only or to treat the cross-over trials as if they are parallel trials. Elbourne states that this approach will produce conservative results as it does not take into account within-patient correlation ([Elbourne 2002](#)). Also each participant will appear in both the treatment and control group, so the two groups will not be independent. We do not plan to combine data from parallel trials with data from cross-over trials; these will be analysed separately.

Dealing with missing data

We contacted the trial authors of the PROACTIVE trial for further data and information, but to date have received no response ([PROACTIVE 2012](#)).

Should further trials be included in future updates, we will seek data for an intention-to-treat analysis, that is, data on the number of participants by allocated treated group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow-up.

Assessment of heterogeneity

Should further trials be included in future updates, we will assess clinical heterogeneity by examining the characteristics of the trials; the similarity between the types of participants, the interventions and the outcomes as specified in the criteria for included trials. Statistical homogeneity will be assessed using a chi-squared test and the I^2 statistic ([Higgins 2003](#)). We will use the following guidelines will be used for the interpretation of the I^2 values ([Deeks 2011](#)):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

Should further trials be included in future updates, in order to assess publication bias we will follow the recommendations on testing for funnel plot asymmetry only if there are at least 10 trials as described in section 10.4.3.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Sterne 2011](#)). If we detect asymmetry in the funnel plot, then we will investigate other possible causes.

The authors will compare the protocol to the full trial publication to identify any reporting bias and therefore ensure that all outcomes measured are reported. If the full protocol is not available, we will at least compare the methods section of the full publication to the results section to ensure that all outcomes measured are reported.

Data synthesis

Should further trials be included in future updates, for the synthesis and meta-analysis of any quantitative data we will use the fixed- and random-effects models as appropriate. If we establish that there is significant heterogeneity between the trials we will use the random-effects model.

In the event that there are insufficient clinically homogeneous trials for this intervention or insufficient trial data that can be pooled a narrative synthesis will be presented.

Subgroup analysis and investigation of heterogeneity

In order to investigate any heterogeneity identified, we plan to carry out subgroup analyses based on:

1. age (children up to 18 years versus adults 18 years and older);
2. SCD with thalassaemia versus those without thalassaemia;

3. severity of SCD
 - a. severity will be assessed by using a Sickle Cell Severity Scale Scoring system when mentioned by trials
 - b. clinical severity as mid, moderate or severe when mentioned by trial.

Sensitivity analysis

If there are sufficient included trials, we intend conducting sensitivity analyses to assess the robustness of our review results by repeating the analysis with the following adjustments: exclusion of quasi-randomised trials; exclusion of trials with unclear or inadequate allocation concealment; exclusion of trials with no or unclear blinding of outcomes assessment; and unclear or inadequate completeness of follow-up.

RESULTS

Description of studies

Results of the search

The search strategy retrieved 112 references. After examination of the titles and abstracts of them, we disregarded 10 references. Full text copies of the the remaining references were obtained and assessed independently by two authors. Any disagreement on the eligibility for this review was resolved through discussion and consensus. Further examination of the remaining 102 references (to six trials) resulted in us excluding five trials (98 references) and including one trial (four references).

Included studies

One trial was eligible for inclusion in the review ([PROACTIVE 2012](#)). Please refer to the '[Characteristics of included studies](#)' for further information on this trial.

While in the multicentre PROACTIVE trial 237 people were enrolled (169 SCC, 42 SC, 15 S β^0 -thalassaemia, 11S β^+ -thalassaemia); the majority were recruited to an observational arm and only ten participants met the inclusion criteria for randomisation ([PROACTIVE 2012](#)). Of these, four were randomised to the transfusion arm and received a single transfusion of 7 to 13 mL/kg packed red blood cells (PRBC), and six were randomised to standard care. None of the four participants who received packed red blood cells developed acute chest syndrome, while 33% (two participants) developed acute chest syndrome in standard care arm.

Excluded studies

We excluded five trials ([Doluee 2019](#); [DOVE 2017](#); [SIT 2014](#); [STOP 1998](#); [Styles 2006](#)). These studies did not meet our inclusion criteria and noted the reasons for their exclusion are available in the '[Characteristics of excluded studies](#)' table.

Risk of bias in included studies

One clinical trial was included in this review; this trial had some limitations with regard to the randomised component of the study ([PROACTIVE 2012](#)). No information on any domain of risk of bias was provided in the published papers. The first and main limitation was the small number of participants, so the trial would obviously be judged to have a high risk of bias given the lack of people recruited. The randomised component of this study provided only a little

information. Also the impact of fluid administration on the course of a pain episode in different centres is unknown. Further restriction of fluid by investigators among clinical centres might further reduce the incidence of nosocomial ACS.

Effects of interventions

One trial was eligible for inclusion in the review ([PROACTIVE 2012](#)). The effects of blood transfusions for treating acute chest syndrome could not be determined from the one very small eligible trial; there were no sufficient data that could be presented within this review. Therefore the synthesis and meta-analysis of quantitative data were not performed.

DISCUSSION

Summary of main results

The comprehensive search in this review provided only one eligible trial. The trial was a feasibility study consisted of an observational arm and a randomised arm (10 participants). Therefore there is not enough evidence to support the effectiveness of blood transfusions for treating acute chest syndrome ([PROACTIVE 2012](#)).

Overall completeness and applicability of evidence

Although the PROACTIVE trial was multi-institutional, involving centres with large sickle cell populations and high expertise in the care of this population, the small numbers of people with SCD enrolled in the PROACTIVE randomised clinical trial precluded any assessment of the effectiveness of blood transfusion to prevent acute chest syndrome in this population.

Quality of the evidence

The risk of bias of the included trial is unclear and the numbers recruited were very small with no data available on any of the reviews pre-defined outcomes.

Agreements and disagreements with other studies or reviews

Over the last 20 years there have been a number of relevant studies one of which was the STOP trial which sought to illustrate the effectiveness of blood transfusions for prevention of stroke ([Adams 1998](#)). Although this randomised controlled trial focused on blood transfusions for prevention of first stroke it also provided some limited data on the possible impact of blood transfusions on reducing the incidence of ACS, but questions still remain unanswered as to whether treatment options for ACS based on these interventions can be considered both effective and safe. No firm conclusions can be drawn at the present time about the effectiveness or otherwise of blood transfusions. In line with this trial, a few trials were enrolled by the title of Post-STOP, which aimed to follow-up the included Sickle Cell Childrens from different points of view. Another comprehensive trial was designed as Silent Cerebral Infarct Transfusion Trial Cohort (SIT), in children with Sickle Cell Anemia. The main outcome of this study was the efficacy of blood transfusion therapy for prevention of recurrent silent cerebral infarcts in participants with SCA. This outcome was far from the aims of our systematic review. Also the Silent Cerebral Infarct Transfusion Trial (SIT) tested the following hypothesis: prophylactic blood transfusion therapy in children with SCI result in at least an 86% reduction in the rate of subsequent overt strokes or new or progressive cerebral infarcts as defined by magnetic resonance

imaging (MRI) of the brain. So the outcome and intervention were far from the aims of our systematic review.

AUTHORS' CONCLUSIONS

Implications for practice

Whilst there appears to be some indication that chronic blood transfusion may play a roll in reducing the incidence of acute chest syndrome (ACS) in people with sickle cell disease (SCD) and albeit offering transfusions may be a widely accepted clinical practice, there is currently no reliable evidence to support or refute the perceived benefits of these as treatment options; very limited information about any of the potential harms associated with these interventions or indeed guidance that can be used to aid clinical decision making. Clinicians should therefore base any treatment decisions on a combination of; their clinical experience, individual

circumstances and the unique characteristics and preferences of adequately informed people with SCD who are suffering with ACS.

Implications for research

We found only one very small randomised controlled trial; this is not enough to make any reliable conclusion to support the use of blood transfusion. This review highlights the need of further high quality research in the context of randomised clinical trials to provide reliable evidence for the effectiveness of these interventions for the relief of the symptoms of ACS in people with SCD.

ACKNOWLEDGEMENTS

We would like to thank those on the previous author team who are not involved in this update (Dunia Alhashimi, Zbys Fedorowicz, Fatima Alhashimi) for their work on developing the original review ([Alhashimi 2010](#)).

REFERENCES

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

PROACTIVE 2012

Methods	In a feasibility study, patients hospitalised for pain who developed fever and elevated sPLA2 were eligible for randomisation to transfusion or observation; all others were enrolled in an observational arm. Of 237 enrolled, only 10 were randomised.
Participants	All SCD patients (Hb SS, SC or S-β0 or S-β+ thalassaemia) aged ≥ 2 years who were admitted to the hospital with acute pain and no evidence of ACS were asked to participate in the screening/observational protocol.
Interventions	A randomised interventional trial of transfusion vs standard care such that: a) consent to the trial and randomisation occurred within 8 hours of eligibility determination; b) initiation of the experimental transfusion occurred within 14 hours of eligibility determination; and c) 40 subjects could be randomised in 12 months.
Outcomes	Chest pain, fever, respiratory and heart rate, reported sites of pain, breath signs.
Notes	This feasibility study for PROACTIVE included two design components: Component 1: the PROACTIVE randomised controlled interventional trial protocol with a target enrolment of 40 participants (20 in each treatment group); and Component 2: an observational cohort consisting of an estimated 300 subjects ineligible for the interventional trial, either because they failed to meet randomisation criteria or developed ACS prior to randomisation. The trial duration was to be 13 months, with an expected recruitment of 40 randomised participants in 12 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided.
Selective reporting (reporting bias)	Unclear risk	No information provided.
Other bias	High risk	Only 10 participants were randomised.

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

Study	Reason for exclusion
Doluee 2019	In this double-blind, randomised clinical trial, 92 people with SCD were recruited who referred to the Emergency Department of a university-affiliated hospital, in Mashhad, Iran, from December 2016 to May 2017. The patients were randomly assigned to two groups of ketorolac and morphine injections for relieving pain crisis according to the clinical conditions of the individuals. So the outcome and intervention were far from the aims of our systematic review.
DOVE 2017	A multinational trial of prasugrel for sickle cell vaso-occlusive events in participants aged 4 to < 18 years in Africa, the Americas, Europe, and the Middle East. The aims of this study were far from the aims of our systematic review.
SIT 2014	The Silent Cerebral Infarct Transfusion Trial (SIT) tested the following hypothesis: prophylactic blood transfusion therapy in children with SCI result in at least an 86% reduction in the rate of subsequent overt strokes or new or progressive cerebral infarcts as defined by MRI of the brain. So the outcome and intervention were far from the aims of our systematic review.
STOP 1998	The Stroke Prevention Trial in Sickle Cell Anemia (STOP) (and the following Optimizing Primary Stroke Prevention in Sickle Cell Anemia (STOP 2)) established routine TCD as standard of care. The intervention and outcome was far from the aims of our systematic review.
Styles 2006	"Trial was designed to determine if red blood cell transfusion can be used to prevent ACS". Participants enrolled with vaso-occlusive pain episodes. A vaso-occlusive pain episode was defined as hospitalisation for pain requiring parenteral narcotics. Unclear if at enrolment participants had ACS.

ACS: acute chest syndrome

MRI: magnetic resonance imaging

SCD: sickle cell disease

SCI: silent cerebral infarct

TCD: transcranial Doppler ultrasound

APPENDICES

Appendix 1. Search strategies - trials registries

Registry	Search terms
ClinicalTrials.gov	Search terms: Acute Chest Syndrome OR Blood OR Transfusion AND Sickle Cell Disease Study type: Interventional Studies Condition: Chest Pain OR Fever OR Mortality Phase: 3
WHO ICTRP	Condition: Chest Pain OR Fever OR Mortality Intervention: simple transfusion OR exchange transfusion OR standard care Recruitment status: ALL

(Continued)

Iranian Registry of Clinical Trials

Search Terms : Acute Chest Syndrome OR Blood OR Transfusion AND Sickel Cell Disease AND Iran

WHAT'S NEW

Date	Event	Description
15 January 2020	New search has been performed	Searches undertaken for this update identified one newly excluded trial (Doluee 2019), additional references to already excluded trials have also been added to the review.
15 January 2020	New citation required but conclusions have not changed	Minor changes have been made throughout all sections of the review.

HISTORY

Protocol first published: Issue 2, 2009

Review first published: Issue 1, 2010

Date	Event	Description
25 July 2016	New citation required but conclusions have not changed	While a new very small trial has been included in the review, this is not enough to make any reliable conclusion in relation to blood transfusions for treating acute chest syndrome in people with sickle cell disease. This review highlights the need of further high quality research to be undertaken.
25 July 2016	New search has been performed	One very small randomised controlled trial has been included in the review (PROACTIVE 2012). No data were available for inclusion in the review. Sections throughout the review have been updated following the inclusion of the eligible trial.
5 August 2013	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Haemoglobinopathies Trials Register identified three potentially relevant trials, however, none were eligible for inclusion in the review.
2 August 2013	New citation required but conclusions have not changed	The review has been updated with minor changes made throughout.
8 September 2011	New search has been performed	A search for potentially relevant trials identified two trials, both of which were excluded on title alone.
28 March 2008	New citation required and major changes	Substantive amendment

CONTRIBUTIONS OF AUTHORS

2015 and 2019 review versions

Roya Dolatkhah conducted a computerized literature search, extracted data from papers, edited the manuscript text and tables, updated the included and excluded references.

Saeed Dastgiri reviewed the potentially relevant studies, appraised the quality of papers, and edited the manuscript.

2010 review version

Dunia Al-Hashimi (DH) and Fatima Al-Hashimi (FAH) were responsible for:

Designing the review

Co-ordinating the review

Performing previous work that was the foundation of this current study

Data collection for the review

Screening search results

Screening retrieved papers against inclusion criteria

Appraising quality of papers

Extracting data from papers

Obtaining and screening data on unpublished trials

Entering data into RevMan

Analysis of data.

Zbys Fedorowicz (ZF) Saeed Dastgiri (SD) and Mona Nasser (MN) were responsible for:

Organising retrieval of papers

Providing additional data about papers.

In future updates DH, FAH, ZF, SD and MN will be responsible for interpretation of the data and writing the review.

DH conceived the idea for the review and is the guarantor for the review.

DECLARATIONS OF INTEREST

There are no financial conflicts of interest and the review authors declare that they do not have any associations with any parties who may have vested interests in the results of this review.

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Internal sources

- N/A, Other.

External sources

- National Institute for Health Research, Other.

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INDEX TERMS

Medical Subject Headings (MeSH)

*Blood Transfusion; Acute Chest Syndrome [etiology] [mortality] [*therapy]; Anemia, Sickle Cell [*complications]; Randomized Controlled Trials as Topic; Treatment Outcome

MeSH check words

Child; Humans