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

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**ABSTRACT**

This is the protocol for a review and there is no abstract. The objectives are as follows:

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

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 (Aaltonen 2005; El-Hazmi 1998; Flemming 1989; Loureiro 2005). Annually, worldwide, there are approximately 275,000 SCD affected conceptions or births (Modell 2008).

Abnormal haemoglobin genes are inherited 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-thalassaemia 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−thalassaemia and sickle cell/β+ thalassaemia (Sβ− and Sβ+). Homozygous sickle cell (SS) disease and sickle cell/β−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; Setjeant 1995).

Acute chest syndrome (ACS) is a frequent complication of sickle cell anaemia, 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 this complication 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, tachypnea, 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 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.

Treatment options

Acute chest syndrome is a frequent and potentially fatal pulmonary illness in SCD. Management of ACS depends on the individuals’ clinical condition and presenting complaint. Standard treatment is intravenous hydration to maintain the individuals’ euolemic 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, dexamethasone (Bernini 1998) and inhaled nitrous oxide (Al Hajeri 2008; Martini-Carvalal 2007; Knight-Madden 2003). In SCD, transfusion may prevent complications (Emre 1995). There are two modalities of red cell transfusion, simple and partial exchange transfusion. The vast majority of transfusions for SCD are simple red cell transfusions, which consist of packed red cells administered intravascularly. Simple transfusions are useful when added oxygen capacity is needed and in conditions where the haemoglobin has dropped to a level significantly below the steady state (Swedlow 2006).

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. Red cell exchange transfusion is an effective but perhaps under utilised treatment for both acute and chronic complications of SCD. Partial exchange transfusion goal 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%.

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; Sβ0; Sβ; Sβ+ (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 will be 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, tachypnea, dyspnea, or new-onset hypoxia (Vichinsky 2000).

Types of interventions
Simple and red cell exchange transfusions during the ACS period will 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
   i) intensity (expressed as scores obtained through any validated patient reported outcomes instrument either generic or SCD specific)
   ii) duration from time of start of symptoms
2. Fever (difference in duration of fever in the different treatment groups)
3. Mortality

Secondary outcomes
1. Duration of any assisted ventilation
2. Duration of hospitalisation in the intensive care unit (ICU): the number of inpatient days
3. Mean duration of opioid therapy
4. Laboratory investigations: concentration of haemoglobin S, pulmonary function tests
   i) 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 will report 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 will identify relevant trials from the 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 quarterly 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 Cochrane Cystic Fibrosis and Genetic Disorders Group Module.

Searching other resources
The reference lists of any clinical trials identified will be cross checked and the review authors' personal databases of trial reports will be examined in an attempt to identify any other relevant trials. We will also attempt to contact investigators of included trials by either conventional or electronic mail to ask for details of additional published and unpublished trials. There will be no language restrictions on included trials and we will arrange to translate and report any relevant non-English papers.

Data collection and analysis
Selection of studies

Two authors, Dunia Al-Hashimi (DH) and Fatima Al-Hashimi (FH), will independently assess the abstracts of trials identified from the searches. We will not be blinded to either the author or journal names. We will obtain full copies of all relevant and 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. We will assess the full text of the papers independently and resolve any disagreement on the eligibility of trials through discussion and consensus; or if necessary through a third party, Zbys Fedorowicz (ZF). After assessment, the authors will eliminate from further review any remaining trials that do not match the inclusion criteria and note the reasons for their exclusion in the ‘Characteristics of excluded studies’ table.

Data extraction and management

Trial details and outcomes 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 ‘Comparisons and data table’ in RevMan 5.0 and automatically checked for differences (RevMan 2008). Dunia Al Hashimi will hold the master copy. Data will only be included if there is an independently reached consensus. Any disagreement 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: 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 assess the clinical homogeneity 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. The clinical outcomes include chest pain, fever, hypoxia, and pallor. The clinical indicators used to monitor the syndrome includes improvement in oxygen saturation and alleviation of presenting symptoms.

Assessment of risk of bias in included studies

Each 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 5.0 (Higgins 2008). 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.

Assessment will be made of the following domains.

1. Randomisation

We will assess this as 'Yes' (i.e. low risk of bias), 'Unclear' (uncertain risk of bias), or 'No' (i.e. high risk of bias). Those assessed as 'Yes' will include, for example, 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 as 'Unclear', trials stated as being randomised, but where no description of the methods used to allocate participants to treatment group was described. We will judge as 'No' methods of randomisation such as use of case record number, date of birth, or alternate numbers.

2. Concealment of allocation

We will assess this as 'Yes' (i.e. low risk of bias), 'Unclear' (uncertain risk of bias), or 'No' (i.e. high risk of bias). Those assessed as 'Yes' will include use of a central independent randomisation unit or sequentially numbered sealed opaque envelopes. We will assess as 'Unclear' if 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 as 'No' if there was an open allocation sequence and the participants and trialists could potentially foresee the upcoming assignment.

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

We will assess this as 'Yes' (i.e. low risk of bias), 'Unclear' (uncertain risk of bias), or 'No' (i.e. high risk of bias). Those assessed as 'Yes' 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 as 'Unclear' where there is insufficient information to permit judgement of 'Yes' or 'No' or where the trial did not address the outcome. We will judge as 'No', for example, 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

We will assess this as 'Yes' (i.e. low risk of bias), 'Unclear' (uncertain risk of bias), or 'No' (i.e. high risk of bias). Those assessed as 'Yes' will include 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 were this outcome was not addressed and where

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there was insufficient reporting of attrition or exclusions, or both, to permit judgement of 'Yes' or 'No'. We will judge as 'No', for example, where reasons for missing data are likely to be related to the true outcome, with for example, 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
We will assess this as 'Yes' (i.e. low risk of bias), 'Unclear' (uncertain risk of bias), or 'No' (i.e. high risk of bias). Those assessed as 'Yes' will include for example 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' where there is insufficient information to permit judgement of 'Yes' or 'No'. We will judge as 'No', for example, where not all of the trial's pre-specified primary outcomes have been reported; and where one or more reported primary outcomes where not pre-specified (unless clear justification provided).

Measures of treatment effect
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 RevMan 5.0 and report the results according to Cochrane Collaboration criteria (RevMan 2008).

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
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.

Dealing with missing data
We planned to 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
We plan to 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, where $I^2$ values over 50% indicate moderate to high heterogeneity (Higgins 2003).

Assessment of reporting biases
If sufficient RCTs are identified, an attempt will be made to assess publication bias using a funnel plot (Egger 1997). If we detect asymmetry in the funnel plot, then we will investigate other possible causes.

Data synthesis
For the synthesis and meta-analysis of any quantitative data we will use the fixed- and random-effects models as appropriate. If it is established 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;
2. SCD with thalassemia;
3. severity of SCD.

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.

ACKNOWLEDGEMENTS
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**Additional references**

Al Hajeri 2008

Alvim 2005

Bernini 1998

Castro 1994

Egger 1997

El-Hazmi 1998

Emre 1995

Flemming 1989

Gladwin 1999

Golden 1998

Higgins 2003

Higgins 2008

Knight-Madden 2003

Loureiro 2005

Marti-Carvajal 2007

Modell 2008

Njamnshi 2006

RevMan 2008

Serjeant 1995

Swerdlow 2006

Taylor 2004

Vichinsky 1997

Vichinsky 2000

* Indicates the major publication for the study
HISTORY

Protocol first published: Issue 2, 2009

28 March 2008 New citation required and major changes Substantive amendment

CONTRIBUTIONS OF AUTHORS

Dunia Al-Hashimi (DH) and Fatima Al-Hashimi (FAH) are responsible for:
Designing the review
Co-ordinating the review
Performing previous work that was the foundation of this current study.

Zbys Fedorowicz (ZF) Saeed Dastgiri (SD) and Mona Nasser MN will be responsible for:
Organising retrieval of papers
Writing to authors of papers for additional information
Providing additional data about papers.

DH and FAH will be responsible for:
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

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 will also be 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.