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Research Article

Systematic Review of Blood Transfusion Implications on Primary and Secondary Stroke Prevention in Sickle Cell

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Abstract

Background: Sickle cell disease is an autosomal recessive disorder that results in production of abnormal haemoglobin, and is characterized by chronic haemolytic anaemia, dactylitis, and acute episodic clinical events called 'crises'. Sickle cell disease is most common in sub-Saharan Africa and is associated with lifelong morbidity and reduced life expectancy.

Aim of the study: Our objective was to synthesize the published literature on the risks and benefits of chronic blood transfusion regimens in patients with sickle cell disease for primary and secondary stroke prevention.

Methods: The present review included relevant randomized controlled trials (RCTs) that investigated the in Medline (via Pubmed), Cochrane Library and Embase. Randomised controlled trials comparing red blood cell transfusions as prophylaxis for stroke in people with sickle cell disease to alternative or standard treatment. There were no restrictions by outcomes examined, language or publication status. The primary Identification of papers and data extraction were performed by independent researchers.

Results: We included four trials (470 participants) published between 1998 and 2014. Four of these trials were terminated early. The vast majority of participants had the haemoglobin (Hb) SS form of sickle cell disease. Two trials compared regular red cell transfusions to standard care in primary prevention of stroke: two in children with no previous long-term transfusions; and one in children and adolescents on long-term transfusion. Two trials compared the drug hydroxyurea (hydroxycarbamide) and phlebotomy to long-term transfusions and iron chelation therapy: one in primary prevention (children); and one in secondary prevention (children and adolescent).The quality of the evidence was very low to moderate across different outcomes according to GRADE methodology. This was due to the trials being at a high risk of bias due to lack of blinding, indirectness and imprecise outcome estimates.

Conclusion: Long-term red cell transfusions proved to reduce the risk of stroke for children who are at higher risk of stroke and have not had previous long-term transfusions (moderate quality evidence), while switching to hydroxyurea with phlebotomy showing little or no effect on the liver iron concentrate was supported by a Low quality evidence. In secondary prevention of stroke there is low-quality evidence as well that switching to hydroxyurea with phlebotomy increases the risk of sickle cell disease-related events. All other evidence in this review is of very low quality.

Keywords: *Anemia; Sickle Cell; Genetics; Hb S; Hemoglobin; Sickle; Public Health; Blood Transfusion; Hydroxyurea*

Introduction

The term "sickle cell disease" refers to a collection of autosomal recessive genetic disorders characterized by the Hb S variant of the P-globin gene. 2 Inherited autosomal recessively, either two copies of Hb S or one copy of Hb S plus another β-globin variant (such as Hb C) are required for disease expression. Hb S carriers are protected from malaria infection, and this protection probably led to the high frequency of Hb S in individuals of African and Mediterranean ancestry. Despite this advantage, individuals with sickle cell disease exhibit significant morbidity and mortality. Symptoms include chronic anemia, acute chest syndrome, stroke, splenic and renal dysfunction, pain crises, and susceptibility to bacterial infections. Pediatric mortality is primarily due to bacterial infection and stroke. In adults, specific causes of mortality are more varied, but individuals with more symptomatic disease may exhibit early mortality. Disease expression is variable and is modified by several factors, the most influential being genotype. Other factors include β-globin cluster haplotypes, α-globin gene number, and fetal hemoglobin expression. In recent years, newborn screening, better medical care, parent education, and penicillin prophylaxis have successfully reduced morbidity and mortality [1,2].

Therapeutic interventions for SCD include: infection prevention by prophylactic antibiotics in the younger population, vaccinations, folic acid supplementation, blood transfusions in combination with iron chelation therapy, hydroxycarbamide and antihypertension treatment. An important part of treatment regimens consists of extensive patient education on the importance of: antibiotic prophylaxis, recognition of provoking risk factors for painful sickle cell crises, early disease symptoms and complications, lifestyle modifications as well as the inheritance of the disease.

Delivering adequate medical care for SCD patients is often difficult due to the fact that most patients present themselves when disease symptoms have already progressed and exhibit poor adherence to medication and medical visits, due to diverse patient related factors which are not easily influenced [3,4]. An important factor of treatment, and by consequence prognosis, is "self-efficacy". Self-efficacy is defined as confidence in one's own capabilities to manage illness. Importantly, it is modifiable as shown by various studies [3,5-7]. An innovative form of outpatient contact to improve self-efficacy is a protocolized Group Medical Appointment (GMA), in which a protocolized Individual Medical Appointment (IMA; care-as-usual) is incorporated within a group consultation, in the presence of fellow patients and other medical professionals [8,9] (Table 1).

	Group medical appointment	Individual medical appointment
Number of patients	6 – 8	1
Duration of appointment	90 min total	15 min per professional
Severity of disease	Various severities of disease	One severity of disease
Professionals	Treating physician, nurse, clinical geneticist, social worker	Treating physician, nurse, clinical geneticist, social worker
Clinical examination	Behind a screen in conference room or in another room (before or after the appointment)	In physician's office
Privacy	Confidentiality protected by the group	Completely

Table 1: *Characteristics of the individual- and group medical appointments.*

Description of the intervention

The focus in the past has largely been on secondary prevention with long-term transfusion, as risk factors for first stroke were not well established. However, with the technological breakthrough of the use of TCD cerebral blood flow velocity measurement, screening has become feasible and is currently the standard of care. Abnormally high blood flow in one or more major arteries is associated with vascular narrowing and predicts an increased risk of stroke, allowing preventative treatment (i.e. long-term red cell transfusion programme) prior to the first stroke [10]. The fetal haemoglobin (HbF) stimulating drug hydroxyurea has been substituted successfully for long-term

red cell transfusion for the prevention of secondary stroke in a limited number of cases [11]. Serial phlebotomy may be highly effective in the reduction of iron overload if transfusions are no longer necessary [12].

As well as the direct and indirect costs, long-term red cell transfusions can have adverse side effects. Iron overload is a problem and requires daily oral iron chelation with deferasirox or deferiprone (or daily subcutaneous or intravenous infusions with desferrioxamine) to avoid the toxic effects of excess iron [13]. However, compliance with the chelation programmes is often poor, and therefore problems of iron overload are potentially serious. Alloimmunisation occurs when the individual develops antibodies to the foreign red cells [14], which is a major problem for future transfusion. Blood products can be contaminated with infective agents such as hepatitis C and HIV, and while this now occurs only rarely in developed countries, the risk is much higher in the developing countries where sickle cell disease is most prevalent. Other problems with transfusions include hyperviscosity of the blood due to over-transfusion, and haemolytic transfusion reactions, both potentially serious side effects. The regimen is often complex and time-consuming, requiring monthly transfusions to maintain the Hb S at approximately 20% to 30%. In short, blood transfusion is a lengthy and costly process which is not without risks, and these must be balanced against the possible benefits prior to embarking on a long-term regimen.

How the intervention might work

Red cell transfusions are undertaken in many people with SCD to dilute the circulating sickle cells, thus reducing the risk of vaso-occlusive episodes and anaemia [15], and increasing tissue oxygen delivery. Transfusions can be given acutely, in emergency treatment of complications such as acute splenic sequestration, aplastic crisis, and acute chest syndrome (ACS), and are also frequently used in preparation for surgery. In addition, many people with SCD receive chronic transfusion regimens in an attempt to prevent severe vaso-occlusion and stroke [14].

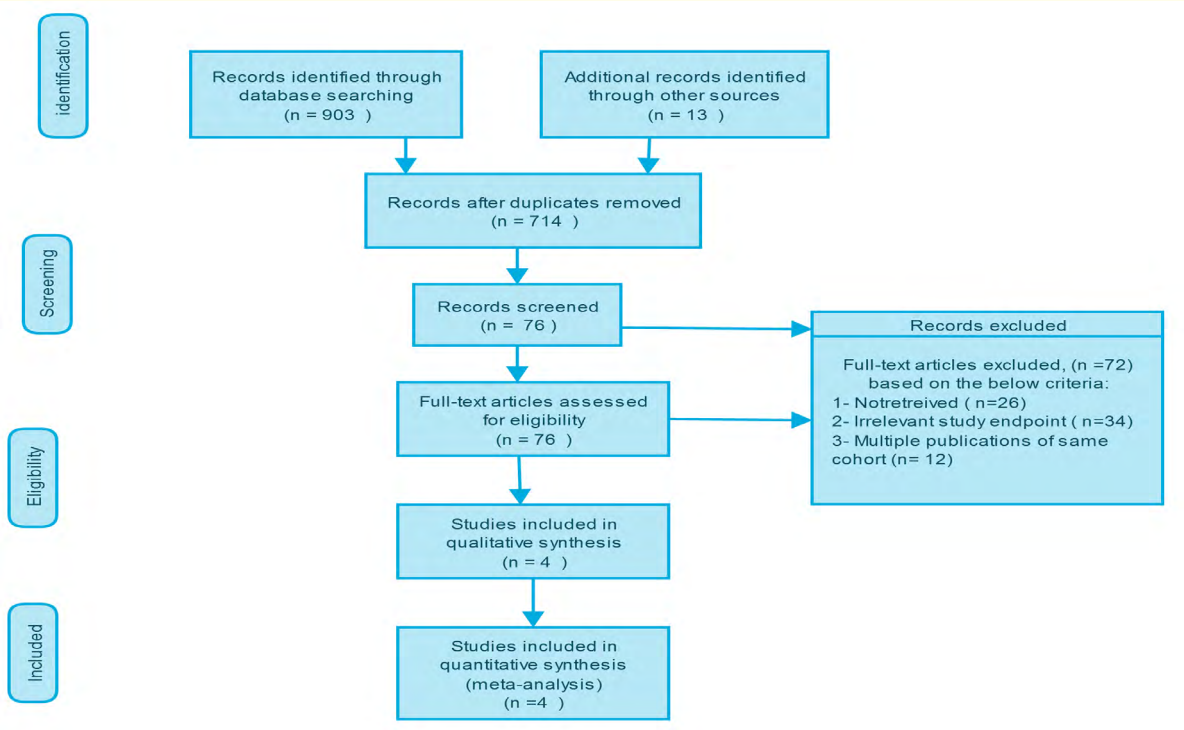
The mechanisms for the reduction in stroke risk from long-term red cell transfusion are not known [16]. However, a reduction in cells containing high amounts of Hb S or an increase in Hb level could have beneficial effects on cerebral blood vessels or interactions between red blood cells and endothelial cells [17]. Transfusion does have an immediate haemodynamic effect measured by reduction of middle cerebral artery velocity [18].

Hydroxyurea is currently the only approved therapeutic drug for the treatment of sickle cell anaemia (for adults with severe vaso-occlusive episodes of pain or acute chest syndrome) and its use has become widespread in both children and adults with this condition. In preliminary studies it was substituted successfully for long-term transfusion in the prevention of secondary strokes, leading to its consideration for use in the phase III SWiTCH trial [12].

For the past three decades the standard treatment for iron overload related to long-term red cell transfusion has been the use of iron chelating agents, including desferrioxamine, deferiprone and deferasirox. Although serial phlebotomy has long been utilized for conditions such as polycythaemia, it has recently been found to be highly effective in the reduction of iron overload from chronic red blood cell transfusion in people who are no longer requiring that treatment [19]. Pilot information on the combination use of hydroxyurea and phlebotomy led to the development of the SWiTCH trial [12].

Methods

Selection criteria of assessed the studies, see PRISMA flow diagram (Figure 1).



Inclusion and exclusion criteria

	Bean CJ., *et al.* (SIT 2014)	**Abboud M., *et al.* (STOP 1 1998)**
Methods	Multicentre randomised trial in 29 clinical centres in the USA, Canada, France and the UK. Recruitment: December 2004 to May 2010. The last participant enrolled completed the exit visit on July 29, 2013.	Multicentre randomised controlled trial conducted in 12 centres in the USA and Canada in children 2 - 16 years of age with HbSS or HbSβº thalassaemia. Screening began in January 1995 and ended in November 1996. The trial was to run to December 1998 but was stopped in September 1997.
Inclusion Criteria	Children aged 5 to 15 years, confirmed diagnosis of haemoglobin SS or haemoglobin Sβ0 thalassaemia, and at least one infarct-like lesion on the screening MRI scan defined as an MRI signal abnormality that was at least 3 mm in one dimension and that was visible in two planes on fluid-attenuated inversion recovery (FLAIR) T2-weighted images, as determined by agreement of two of the three trial neuroradiologists.	Children 2 to 16 years of age and who had been given a diagnosis of sickle cell anaemia or sickle ß0 thalassaemia at high risk of stroke with a blood flow velocity of at least 200 cm per second on 2 TCD trials.
Exclusion Criteria	History of focal neurologic deficit associated with an infarct on brain MRI, a seizure disorder, treatment with hydroxyurea in the previous 3 months, a history of regular transfusion therapy, or imaging or non-imaging TCD measurement that was above the trial-defined thresholds.	history of stroke, had an indication for or contraindication to long-term transfusion, were receiving other treatments that affected the risk of stroke, were infected with the human immunodeficiency virus (HIV), had been treated for seizures, were pregnant, or had a serum ferritin concentration above 500 ng per millilitre.

Table 2: *Methods and Inclusion and exclusion criteria for study 1 and 2 (SIT 2014 and STOP 1 1998).*

	Bean CJ (SIT 2014)	**Abboud M., *et al* (STOP 1 1998)**
Participants' Profile	Participant flow: 1210 registered for screening; 1074 had screening MRI evaluated by neuroradiology committee; 675 had normal, 20 indeterminate MRI; 379 had infarct-like lesions on screening MRI; 291 had infarct-like lesions adjudicated by neurology committee; 220 had pre-randomisation MRIs adjudicated by neuroradiology committee; 196 underwent randomisation. Transfusion arm: N = 99 (15 crossed over to observation) Sex: male: 59 (60%); F: 40 (40%) Age: 5 to 7: 26 (26%): 8 to 10: 35 (35%); 11 to 13: 32 (32%); 14 to 15: 6 (6%) TCD velocity: median (IQR) cm/sec: 147 (123-168) (N = 98) Lesions on initial MRI: 99 (100%) Parental report of recurring headaches: yes: 37 (37%); No: 62 (63%) Steady state haemoglobin: median (IQR): g/L: 77 (72 to 84) Phenotypes: not stated (Included only HbSS or HbSβº) Hb F% median (IQR): 9.0 (4.0 to 14.0) Alpha thalassaemia: not reported Observation arm: N = 97 (6 crossed over to transfusion) Sex: male: 52 (54%); F: 45 (46%) Age: 5 to 7: 28 (29%): 8 to 10: 32 (33%); 11 to 13: 29 (30%); 14 to 15: 8 (8%) TCD velocity: median (IQR) cm/sec: 143 (131 to 163) Lesions on initial MRI: 97 (100%) Parental report of recurring headaches: yes: 43 (44%); No: 54 (56%) Steady state haemoglobin: median (IQR): g/L: 79 (74 to 89) Phenotypes: not stated trial included only HbSS or HbSβº Hb F% median (IQR): 10.0 (5.0 to 15.0) Alpha thalassaemia: not reported	Participant flow: screened: N = 1934; eligible: N = 206 randomised: N = 130 Transfusion: N = 63 Sex: male: 31 (49%) Age: mean (SD): 8.2 (3.2) years HbS% mean (SD): 87 (10) HbF% mean (SD): 8.0 (5.2) Alpha thalassaemia: 14 (22%) TCD velocity: mean (SD): 223 (27) cm/sec Lesions on initial MRI: N (%) participants: 19 (31%) Standard care: N = 67 Sex: male: 29 (43%) Age: mean (SD): 8.4 (3.3) years HbS% mean (SD): 87 (7) HbF% mean (SD): 9.4 (5.0) Alpha thalassaemia: 7 (9%) TCD velocity: mean (SD): 223 (28) cm/sec Lesions on initial MRI N (%): participants 25 (38%) Phenotypes: not reported (trial included only HbSS or HbSβº)

Table 3: *Clinical Profile for the participates in the included study 1 and 2.*

	Abboud MR., *et al.* (STOP 2 2005)	**Alvarez O., *et al.* (SWiTCH 2012)**
Methods	Multicentre RCT, extension to the STOP trial conducted in 23 centres (including the 12 centres in STOP) in the U.S. and Canada to determine whether regular blood transfusions for the prevention of stroke could be stopped in children and youth 5 - 20 years of age with SCD.The trial was meant to be a 54-month trial involving 50 participants in each group, with 60 of the participants enrolled during the first 12 months and 40 during the next 24 months; after recruitment ended, there were 18 months of follow-up. The trial was stopped on the advice of the data safety and monitoring committee because of concern about safety at the fourth interim analysis with 79 participants enrolled.	Multicentre randomised controlled non-inferiority trial conducted in 26 paediatric sickle cell centres in the USA. Total duration of trial treatment was 30 months after randomisation, with a final trial visit scheduled 6 months after discontinuation of trial treatments.
Inclusion Criteria	Children whose Doppler studies normalized after 30 or more months of transfusion were eligible for the present trial. In addition, children who had not participated in the previous STOP trial whose condition met the criteria for eligibility and treatment were also eligible for the present trial. Adequate participation in a transfusion program (≥ 24 transfusions in 30 months and Hb S < 30% in at least 20 of the 30 months); 2 Normal TCD examinations at least 2 weeks apart while receiving transfusions within 4 months of randomisation; age, 5 to 20 years; consent to participate in trial.	Paediatric participants with severe forms of SCA (HbSS, HbS/βº-thalassemia, HbS/OArab); age range of 5.0 to 18.9 years, inclusive, at the time of enrolment; completed overt clinical stroke after the age 12 months with documented infarction on brain CT or MRI; at least 18 months of chronic monthly erythrocyte transfusions since primary stroke; transfusional iron overload, a previously documented liver iron concentration ≥ 5.0 mg Fe per g of dry weight liver or serum ferritin ≥ 500 ng/mL on 2 independent measurements; adequate monthly erythrocyte transfusions with average HbS ≤ 45% (the upper limit of the established academic community standard) for the past 6 months before enrolment; parent or guardian willing and able to provide informed consent with verbal or written assent from the child (< 18 years of age), and subject willing and able to provide informed consent (≥ 18 years of age); ability to comply with trial related treatments, evaluations, and follow-up.
Exclusion Criteria	Prior stroke; Indication for chronic transfusion; contraindication for chronic transfusion; moderate-to-severe intracranial arterial disease on MRA.	inability to receive or tolerate chronic RBC transfusion therapy; inability to take or tolerate daily oral hydroxyurea; clinical and laboratory evidence of hypersplenism (temporary); abnormal laboratory values at initial evaluation (temporary); current participation in other therapeutic clinical trials; current use of other therapeutic agents for sickle cell disease (e.g. arginine, decitabine, magnesium); any condition or chronic illness, such as a positive tuberculin (PPD) test, which in the opinion of the investigator makes participation ill-advised; inability or unwillingness to complete required screening studies, including blood tests, brain MRI/MRA, and liver biopsy; a sibling enrolled in SWiTCH.

Table 4: *Methods and Inclusion and exclusion criteria for study 3 and 4 (SIT 2014 and STOP 1 1998).*

	Abboud MR., *et al.* (STOP 2 2005)	**Alvarez O., *et al.* (SWiTCH 2012)**
Participants' Profile	Participant flow: screened: not reported; eligible: not reported; randomised: N = 79. Transfusion continued: N = 38 Sex: male: 20 (53%) Age: mean (SD): 12.5 (3.3) HbS % mean (SD): 21.0 (8.6) HbF% mean (SD): 2.4 (1.8) Alpha thalassaemia: not reported TCD velocity: mean (SD): 139 (16) cm/sec Lesions on initial MRI: 10 (26%) Phenotypes:Not reported (trial included only HbSS or HbSβº) Transfusion halted: N = 41 Sex: male: 13 (32%) Age: mean (SD): 12.05 (3.1) HbS% mean (SD): 19.0 (11) HbF% mean (SD): 2.3 (1.5) Alpha thalassaemia: not reported TCD velocity: mean (SD): 143 (18) cm/sec Lesions on initial MRI: 11 (27%) Phenotypes: not reported (trial included only HbSS or HbSβº)	Participant flow: screened: N = 202; enrolled: N = 161; randomised: N = 134 Transfusion + chelation: N = 66 (one moved before starting trial treatment) Sex: Male: 31 (47%) Age: Mean (SD): 13.3 (3.8) Phenotype: HbSS: 66 (100%) Previous recurrent stroke: 4 (6%) History of TIA: 11 (17%) Infarction: 65 (98%) Vasculopathy: 54 (82%) Moya-moya: 5 (8%) Liver iron content (LIC), mg Fe/g dw liver median (IQR): 14.5 (9.5 to 23.3) Serum ferritin, ng/mL median (IQR): 3282.0 (2321.0 to 4306.0) HbS% median (IQR): 27.0 (21.2 to 38.6) HbF% median (IQR): 1.7 (1.0 to 2.5) Alpha thalassaemia: not reported Hydroxyurea + phlebotomy:N = 67 Sex: male: 41 (61%) Age: Mean (SD): 13.0 (4.0) Phenotype: HbSS: 66 (99%) Previous recurrent stroke: 10 (15%) History of TIA: 10 (15%) Infarction: 65 (98%) Vasculopathy: 53 (79%) Moya-moya: 11 (16%) Liver iron content (LIC), mg Fe/g dw liver median (IQR): 13.9 (8.7 to 22.9) Serum ferritin, ng/mL median (IQR): 3346.0 (2202.0 to 4682.0) HbS% median (IQR): 30.3 (23.8 to 39.6) HbF% median (IQR): 1.4 (0.8 to 2.2) Alpha thalassaemia: not reported

Table 5: *Clinical Profile for the participts in the included study 1 and 2.*

Results

Results of the present study concorded with a recent meta-analysis conducted by Estcourt LJ., *et al* [20].

Intervention and Outcome of the included studies

	Bean CJ (SIT 2014)	**Abboud M., *et al.* (STOP 1 1998)**
Transfusion:	Transfusion: transfusion arm received a transfusion approximately monthly to maintain a target haemoglobin concentration greater than 90 g/L and a target haemoglobin S concentration of 30% or less. Red cell component: leucocyte-depleted, negative for haemoglobin S. Red cell matching: ABO, Rh and Kell antigens. Iron chelation: ferritin levels were monitored before each transfusion. Site investigators were advised to initiate chelation therapy for participants who had ferritin levels greater than 1500 ng per millilitre for 2 or more consecutive months.	Transfusion: N = 63 In the transfusion arm the goal was to reach an HbS concentration < 30 per cent of total haemoglobin within 21 days without exceeding a haemoglobin concentration of 120 g/L and a hematocrit of 36%. Exchange or simple transfusion were allowed: 63% were simple transfusions, 12% were exchange; 25% a combination of simple and exchange. Red cells were delivered in a volume of approximately 10 to 15 mL per kg of packed cells per transfusion. Red cell component: leucocyte-depleted, negative for haemoglobin S. Red cell matching: ABO, Rh and Kell antigens.
Interventions	**Observation:** observation arm received standard care with no treatment for silent infarcts and no hydroxyurea therapy and were evaluated quarterly	Iron chelation: none. Potential participants with a ferritin level above 500 ng/mL were excluded from the trial. The intention was to exclude any child with a significant iron burden before initiation of treatment, thus avoiding clinically significant iron overload during the trial. Standard care:N = 67
Primary Outcome	The recurrence of infarct or haemorrhage as determined by neuroimaging, clinical evidence of permanent neurologic injury, or both. A new infarct had to meet the criteria for a SCI; an enlarged SCI was defined as a previously identified silent cerebral infarct that increased by at least 3 mm along any linear dimension in any plane on MRI; TIA, included in secondary analyses of neurologic outcomes, defined as an event that resulted in focal neurologic deficits that lasted less than 24 hours, did not result in abnormalities on T2-weighted or FLAIR images that were indicative of an acute infarct, and had no other reasonable medical explanation.	Cerebral infarction and intracranial haemorrhage.
Secondry Outcome	Changes in cognition, assessed by measurement of IQ scores with the Wechsler Abbreviated Scale of Intelligence12 or the Wechsler Preschool and Primary Scale of Intelligence III; also assessed scores on the Behavior Rating Inventory of Executive Function (BRIEF).	Death, transfusion-related adverse events.

Table 6: *Explains the different intervention methods and outcome for study 1 and 2 (SIT 2014 and STOP 1 1998).*

	Abboud MR., *et al.* (STOP 2 2005)	Alvarez O., *et al.* (SWiTCH 2012)
Transfusion:	Transfusion continued: n = 38. Transfusion could be simple, manual exchange or automated exchange. antigens. Red cell component: leucocyte-depleted, negative for haemoglobin S. Red cell matching: ABO, Rh and Kell antigens. Iron chelation: chelation therapy with the use of deferoxamine was recommended if serum ferritin levels exceeded 2500 ng per millilitre. Transfusion halted: n = 41.	Standard treatment (transfusion + chelation): N = 66 For standard treatment (blood transfusion + iron chelation) participants received monthly blood transfusions designed to maintain 30% HbS, with local discretion regarding transfusion type (e.g., simple or erythrocytapheresis). Red cell component: not reported. Red cell matching: not reported. Iron chelation: daily iron chelation. Hydroxyurea + phlebotomy: N = 67
Interventions	Participants in the transfusion-halted group could receive transfusions to treat complications of sickle cell disease. Initiation of hydroxyurea therapy or regular transfusion was designated as a cross-over and data was censored on the patient as of the date of treatment	Participants randomised to hydroxyurea + phlebotomy commenced hydroxyurea at 20 mg/kg/d with stepwise escalation to MTD. Transfusions continued for 4 to 9 months during an overlap phase designed to protect against recurrent stroke during hydroxyurea dose escalation. Once MTD was reached and transfusions were discontinued, phlebotomy commenced with a target of 10 mL/kg (maximum volume, 500 mL) blood removed monthly to reduce iron burden.
Primary Outcome	composite end point was a stroke (cerebral infarction or intracranial haemorrhage) or reversion to abnormal velocity on transcranial Doppler ultrasonography, defined as 2 consecutive studies with abnormal velocities, 3 consecutive studies with an average velocity of 200 cm per second or more, or 3 consecutive inadequate studies plus evidence of severe stenosis on MRA.	Composite primary endpoint of secondary stroke recurrence rate and quantitative liver iron concentration.
Secondry Outcome	Deaths, acute chest syndrome and transfusion adverse events.	Non-stroke neurological events, non-neurological sickle cell clinical events, quality of life evaluation, and measures of organ function.

Table 7: *explains the different intervention methods and outcome for study 3 and 4 (SIT 2014 and STOP 1 1998).*

Discussion

This Cochrane Review aimed to evaluate the literature on the effectiveness and safety of red cell transfusions for primary and secondary prevention of stroke Four RCTs the inclusion criteria out of a total of 916 searched studies with 470 participants.

The trials were published between 1998 and 2014. The trials were aimed to compare red cell transfusions to standard care as well as hydroxyurea with phlebotomy to red cell transfusions with chelation. The majority of participants had HbSS sickle cell disease (SCD), all trials included children and no trials included adults for primary or secondary prevention of stroke.

Red cell transfusions versus standard care

Primary prevention

Three randomised trials compared red cell transfusions to standard care for primary prevention of stroke. Two of these trials included children with no previous long-term transfusions; one of these included children with abnormal TCD velocities, and the other included children with silent cerebral infarcts on magnetic resonance imaging (MRI) but normal TCD velocities. The third trial included children and adolescents on long-term transfusion whose TCD velocities had normalised. Two of the three trials were terminated early due to safety concerns.

The findings of the review led to the following main conclusions regarding red cell transfusions versus standard care.

Children with no previous long-term red cell transfusions

- Long-term transfusions probably reduce the incidence of clinical stroke in children with a higher risk of stroke (abnormal TCD velocities or previous history of silent cerebral infarctions (SCIs)).
- Long-term transfusions may: reduce the incidence of other SCD-related complications (acute chest syndrome (ACS) and painful crisis); make little or no difference to IQ scores in children with SCIs; and may increase quality of life.
- We are very uncertain whether long-term transfusions: reduce all-cause mortality (no deaths in either trial); reduce the risk of TIAs; or increase the risk for developing alloimmunisation.

Children and adolescents with previous long-term red cell transfusions and normalised TCD velocities

- We are very uncertain whether continuing red cell transfusions reduces the incidence of clinical stroke or all-cause mortality.

Several review outcomes were only reported in one of the trial arms (SCD-related complications, alloimmunisation, incidence of TIAs), and the trial did not report neurological impairment or quality of life.

Hydroxyurea and phlebotomy versus red cell transfusions and chelation.

Primary prevention in children

- There were no deaths or clinical strokes in either arm of the trial
- Switching to hydroxyurea and phlebotomy may have little or no effect on liver iron concentrations, but may reduce serum ferritin levels.
- We are very uncertain whether switching to hydroxyurea and phlebotomy has any effect on the incidence of TIA, or the risk of other SCD-related complications (ACS or painful crisis)

Secondary prevention in children and adolescents

- Switching to hydroxyurea and phlebotomy may increase the risk of SCD-related serious adverse events
- Switching to hydroxyurea and phlebotomy may have little or no effect on liver iron concentrations, but may reduce serum ferritin levels.
- We are very uncertain whether switching to hydroxyurea and phlebotomy increases the risk of stroke.
- We are very uncertain whether switching to hydroxyurea and phlebotomy has any effect on: all-cause mortality, or the risk of a TIA.

Neither trial reported on neurological impairment, alloimmunisation, or quality of life.

Red cell transfusions versus standard care

No previous long-term red cell transfusions

Clinical stroke in children with higher risk of stroke (abnormal TCD velocities and SCIs), is considered as moderate quality evidence due to indirectness.

However, we considered three outcomes as low quality evidence due to serious risk of bias and indirectness. These were SCD-related adverse events (acute chest syndrome and painful crises), neurological impairment (IQ) and the quality of life.

Likewise, we considered three outcomes to be very low quality evidence due to serious risk of bias, indirectness and imprecision which were all-cause mortality, TIAs and transfusion-related adverse events (alloimmunisation).

Previous long-term red cell transfusions

We considered two outcomes as very low quality evidence due to serious risk of bias, indirectness and imprecision. These were clinical stroke and all-cause mortality.

Several review outcomes were only reported in one of the trial arms (SCD-related complications, alloimmunisation, incidence of TIAs).

The trial did not report neurological impairment or quality of life.

Hydroxyurea and phlebotomy versus red cell transfusions and iron chelation.

Primary prevention

We considered one outcome (transfusion-related adverse events - iron overload) as low quality evidence due to serious risk of bias and indirectness.

We considered four outcomes as very low quality evidence due to serious risk of bias, indirectness and imprecision. These were clinical stroke, all-cause mortality, TIAs and SCD-related adverse events (ACS, painful crises).

The trial did not report neurological impairment or quality of life.

Secondary prevention

We considered one outcome as low quality evidence (transfusion-related adverse events - iron overload) as low quality evidence due to serious risk of bias and indirectness.

We considered four outcomes to be very low quality evidence due to serious risk of bias, indirectness, and imprecision. These were clinical stroke, all-cause mortality, TIAs and SCD-related adverse events.

The trial did not report neurological impairment or quality of life.

Conclusion

Implications for practice

In children with no previous long-term transfusions, red cell transfusions probably reduce the risk of stroke and may confer some additional advantage by reducing the rates of ACS and painful crisis. This must be balanced against the adverse effects and costs of a chronic transfusion regimen. We are uncertain whether transfusions can be stopped in children and adolescents at high risk of stroke who have had their TCD velocities normalised, nor has any treatment duration threshold been established for stopping transfusions.

We are uncertain if switching to hydroxyurea with phlebotomy is non-inferior to red cell transfusions in a select population of children in primary prevention; we are also uncertain as to how long the drug effects may be maintained. We are uncertain if switching to hydroxyurea with phlebotomy results in an increased risk of stroke in secondary prevention and switching may increase the risk of adverse events in children and adolescents. Hydroxyurea with phlebotomy did not demonstrate superiority in iron removal as measured by liver iron concentration.

Due to lack of evidence this review cannot comment on management for adults with HbSS disease or children and adults with HbSß^{0}, HbSC or HbSß$^{+}$ disease.

Implications for research

Information from a well-designed, prospective, randomised controlled trial of chronic blood transfusion regimens in persons with sickle cell disease who have had a previous stroke is desirable in order to make recommendations for the optimal use of this therapy in secondary stroke prevention. Recent improvements in methods of detecting high-risk individuals are improving clinical outcome, but further research is needed to assess the relative risks and benefits of hydroxyurea in comparison with long-term transfusion therapy for primary and secondary prevention of cerebral infarcts. Randomised trials are needed comparing blood transfusions with both standard care and hydroxyurea for both primary and secondary prevention in adults with SCD.

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