Review Articles

Principles of blood transfusion in sickle cell anemia

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ABSTRACT

Sickle cell anemia (SCA) is one of the commonly inherited hemoglobinopathies in the Kingdom of Saudi Arabia. It is characterized by periods of remissions and exacerbations called crises as well as certain pathological phenomenon such as acute chest syndrome, priapism, hepatopathy, and cerebrovascular stroke. Blood transfusion (BT) as therapy and prophylaxis in SCA, although was advocated as early as the 1940's, there are still debates regarding its benefits and risks. This is a review of the value of BT in patients with SCA with emphasis on the risks and benefits as well as guidelines towards safe BT.

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Sickle cell anemia (SCA), which is due to homozygous inheritance of the hemoglobin S (HbS) variant, results from a single amino-acid substitution of valine for glutamic acid in the 6th position among the 146 amino acids of the hemoglobin β-chain. It is one of the common inherited hemoglobinopathies in the Kingdom of Saudi Arabia (KSA). The prevalence of hemoglobin AS (HbAS), and hemoglobin SS (HbSS) in KSA is 7.4% (0-25.9%) and 1.1% (0-5.3%), giving an overall HbS gene frequency of 0.047.[1] The clinical spectrum of this disease is variable, commonly characterized by repeated acute painful episodes, increased vulnerability to infections, and certain pathological phenomena such as acute chest syndrome (ACS), cerebro-vascular strokes, hepatopathy, and multiorgan failure. Packed red blood cells (PRBC) transfusion in SCA was advocated as a therapy and prophylaxis as early as 1940s in acute painful episodes, pregnancy, leg ulcers, and anemia, but there have been debates; however, regarding the benefits and risks of blood transfusion (BT) in various presentations of SCA. One reason for this is that BT may adversely affect patients with SCA by increasing blood viscosity and precipitating vaso-occlusive crisis. These patients are acclimatized to normally live at Hb level between 8 and 10gm/dl, and injudicious BT may subsequently build up the hematocrit and the viscosity of their blood, leading to vaso-occlusive crisis.

The importance of BT as a therapy in patients with SCA, however, needs to be emphasized and guidelines towards safe BT need to be setup taking into consideration the risks, and benefits as well as long-term impact.[2] This is especially so in this era when the life expectancy of patients with SCA is progressively increasing.

Pre-transfusion requirements. Patients with SCA are prone to several complications and at times unexpected medical problems occur and for these reasons they should be diagnosed early. The neonatal Hb identification for sickling hemoglobinopathies is of vast consequence to enable practitioners, at areas of high prevalence of the gene, to recognize those at risk at birth needs to be emphasized. As a baseline, the following should be conducted for each patient: a) Blood grouping, which should include: ABO, Rhesus, Duffy, Lewis, Kell, Kidd, and MNSs systems whenever possible. b) Red blood cell (RBC) transfusion must be from a compatible donor with matched ABO, C, c, D, E, e, and K, k c) To minimize the possibility of developing alloimmunity,

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RBC transfusion should have pre-stored leukocytes depletion through effective filter. d) For patients who develop alloantibodies, cross matching should include at least Fy^a, Fy^b as well as those antigens implicated in the alloantibodies prior to further transfusion. e) Hepatitis B, hepatitis C, human immunodeficiency virus (HIV) serological assays, as well as hepatitis GB-C, transfusion transmitted virus (TTV) whenever possible. f) Vaccination against Hepatitis B, pneumococcal, *Hemophilus Influenzae* and meningococci.

Indications for blood transfusion in sickle cell anemia. The life span of sickle cells is only 15-20 days compared to 120 days for normal red cells, and as a result of this, most patients with SCA have moderate anemia. This may be exacerbated further in the event of complications such as splenic sequestration crisis, hyperhemolysis, infection and aplastic crisis. Whereas it is acceptable to use PRBC transfusion in symptomatic anemic patients who are prone to have a cardiovascular collapse, the indications for BT in patients with SCD are:

I. Definite indications. 1) Symptomatic anemia from any cause such as infection, hemolysis or aplastic crisis. 2) Acute splenic sequestration is defined as a sudden enlargement of the spleen size secondary to rapid sequestration of circulating RBC in the spleen. This may take the form of major crisis characterized by acute rapidly enlarging spleen accompanied with, severe anemia, cardiovascular compromise, reticulocytosis, thrombocytopenia, and granulocytosis, or more commonly the less severe minor crisis.[3] Transfusion of RBC in these cases are necessary to restore vascular volume towards baseline. This is usually followed by reduction in spleen size and elevation of Hb level above steady state. To obviate volume overload, it is advisable to transfuse aliquots of blood on intervals and monitor the Hb level and splenic size. 3) Aplastic crisis is usually associated with parvovirus infection in hyper-dynamic bone marrow as in those with SCA.[4,5] This will result in transient erythroblastopenia and severe anemia, with reticulocytopenia. Spontaneous recovery however is the rule, and judicious RBC transfusion is recommended. In refractory cases with persistent parvovirus B19 infection, immunoglobulins (IgG) 400mg/kg intravenously for 5 days can be used.[6] 4) Hyperhemolytic crisis implies an accelerated RBC destruction, with anemia, elevated bilirubin, lactate dehydrogenase level, and markedly elevated reticulocytes count. It is usually seen in association with infection, and ACS. Simple RBC transfusion or exchange BT is recommended. 5) Management of severe illness. Tissue hypoxia and acidosis may promote sickling of RBCs and vice versa. In these situations exchange BT is beneficial it not only removes cells that can sickle, but also interrupts the cycle of sickling and limits tissue ischemia. (i) Acute chest syndrome is defined as the development of a new pulmonary infiltrate on chest x-ray, caused by infarction, infection or a combination of other etiological factors.[7,8] Although, RBCs transfusion in these patients has not been methodically evaluated, there is however a definite clinical evidence of improvement after BT.[9,10] Red blood cell transfusions may prevent the development of severe pulmonary complications, shorten the illness duration, and reduce mortality. It is acceptable to use simple BT in hypoxic patients or exchange transfusion in those with rapidly deteriorating respiratory status or severe pulmonary insufficiency.[11] (ii) Stroke is one of the major vaso-occlusive complications of SCD, with a high recurrence rate,[12] usually present as sudden neurologic events with hemiparesis, aphasia, seizures, or even coma.[13] Acute treatment of a confirmed or suspected cerebral infarction consists of immediate partial or complete exchange transfusion aiming to reduce the HbS level to 30% and improve blood viscosity. Although, RBCs transfusion does not seem to affect long-term neurological outcome, it has been shown to decrease the recurrence of strokes, by improving perfusion and oxygenation of brain tissue. The tremendous initial outcome of strokes in SCA validates an instantaneous exchange transfusion therapy.[14] The spectacular initial restoration and improved vascular flow on angiography have been reported following exchange transfusion in SCA patients who have had stroke.[14] In these patients exchange BT rather than simple BT is recommended. Chronic RBC transfusion reduces stroke recurrence rate from 40-90% to around 10%.[15] The appropriate duration of transfusion is still unknown. (iii) Severe infections continue to be major causes of morbidity and mortality in SCD. Prior to the era of antibiotics, pneumococcal sepsis was the leading cause of death in children with SCD.[15-17] Nowadays other organisms such as mycoplasma, chlamydia, salmonella and other gram-negative organisms are responsible for serious infections in SCD.[18] While, the role of RBC transfusion in combating severe infection is still controversial, it is advisable to correct exacerbating anemia inpatients with a serious and potentially fatal infection. (iv) Acute multiorgan failure characterized by a rapid clinical deterioration and failure of multiple organs including kidneys, liver, and lungs; which usually progresses to nonfocal encephalopathy. This is thought to be secondary to systemic fat embolization. Red blood cell transfusion, in these situations may yield better survival and restoration of organs function.[19] 6) Prevention of postoperative complications. It is well known that patients with SCD are at increased risk of postoperative complications following major surgical interventions including acute painful episodes, ACS, and to a lesser frequency stroke. To overcome this, several perioperative BT regimens have been adopted ranging from an aggressive preoperative

exchange transfusion in an attempt to reduce Hb S level less than 30% to a simple BT to increase Hb level to 10-12g/dl. Simple BT has been shown to be as good as exchange BT, and associated with less BT related complications.[20,21] It is now a standard practice to give simple BT preoperatively to increase the Hb to 10-12 g/dl in SCD patients undergoing major surgery.

II. Controversial indications. There are clinical situations in which RBCs transfusions are still controversial due to lack of supportive data, or unproven clinical efficacy. 1) Pregnancy in patients with SCD was thought to be associated with poor outcome and as a result of this prophylactic RBCs transfusion was adopted.[22-24] This however was recently challenged, and the current practice is to limit RBCs transfusion to those with frequent complications during pregnancies.[25,26] 2) Acute painful episodes are considered to be secondary to ischemic tissue damage from vaso-occlusion. The proponents of BT in these episodes claim that it will restore the blood flow and shorten the duration and severity of these episodes. This however has never been proven. 3) Acute priapism precipitated by sickling and stagnation of red cells in the corpora, with evidence of low blood flow leading to exaggeration of the normal erectile process of the penis. This sustained painful erection eventually leads to clotting of blood in the corpora resulting in impotence. Red blood cell transfusion has been advocated as a part of the management of this acute distressful condition,[27-29] but the results are however variable.[30,31] 4) Radiological evaluation using contrast media which is hypertonic, makes these patients liable to undergo RBCs hemolysis[32] as well as the development of painful episodes. To overcome this, RBCs transfusion was advocated. The value of this however was not proven. Add to this the availability of safe nonionic contrast media, which makes this practice unnecessary.[33,34]

III. Chronic blood transfusion therapy. It is beneficial to place certain SCD patients, who are confronted with specific complications, on chronic BT therapy. This regimen however is accompanied with complications such as the risk of blood-transmissible infections, alloimmunization, and iron overload. 1) Primary stroke prevention and obviating recurrence of stroke by chronic BT has been proven to be valuable for those with abnormal blood flow velocity in their internal carotid and middle cerebral arteries as measured by transcranial doppler studies.[35] The aim should be to reduce the hemoglobin S level below 30%.[14,36] The duration of this transfusion program however is not well established, and stroke recurrence was reported to occur as late as 12 years after the attack.[37] The availability of new emerging line of therapy, like hydroxyurea,[38-41] makes it necessary to discuss with the patient and family the advantages and disadvantages of each treatment modality. 2) Acute chest syndrome. The value of BT in decreasing the frequency and severity of recurrent attacks of ACS has been proven clinically, although there are no controlled clinical trials. Chronic blood transfusion is recommended for those with pulmonary hypertension and chronic hypoxia. Hydroxyurea is also a valuable drug in preventing recurrence of ACS, and this option should be discussed with the patient.[42]

IV. Controversial indications of chronic blood transfusion in sickle cell anemia. There are anecdotal reports of favorable utilizations of chronic transfusions in recurrent priapism,[43] in those with silent cerebral infarcts on magnetic resonance angiographic findings, in those with leg ulcers, and intrahepatic cholestasis, but there are no clinical trials to support this.

Complications. In patients with SCA PRBCs are the preferred blood component for transfusion, and leukocyte reduced PRBCs should be used due to their beneficial effects in reducing hemolytic transfusion reactions, febrile reactions, nonhemolytic transfusion reactions, transmission of infections, alloimmunization, and platelet refractoriness. Blood of those with sickle cell trait, however, functions normally and can be used for transfusion unless a targeted reduction in HbS level is intended.

Table 1 - Annual rates of red cell loading, red cell exposure, and iron loading: erythrocytapharesis versus simple transfusion.

Transfusion protocol	Net RBC (ml of RBC/kg/yr)	Mean net iron load (mg iron/kg/yr)	Range of net iron load (mg iron/kg/yr)	PRBC use RBC/kg/yr
Erythrocytapharesis HbS<50%	17.8 ± 12.9	19.4 ± 14	6-50	214.6 ± 45.0
Modified simple HbS<50%	99.4 ± 37.7	107.0 ± 41	76-171	132.8 ± 49.5
Conventional simple HbS<30%	133.0 ± 29.3	144.0 ± 32	116-210	176.9 ± 39.3
RBC - red blood cells, PRBC - packed red blood cells, HbS - hemoglobin S, yr - year				

Table 2 - Manual exchange transfusion procedure to achieve <50% hemoglobin S in an average sized adult with pre-exchange hematocrit of approximately 25%.

Phlebotomize 500 ml whole blood
Infuse 300 ml normal saline
Infuse 2 U PRBCs
Phlebotomize 500 ml whole blood
Infuse 300 ml normal saline
Infuse 2 U PRBCs
Determine post-transfusion hematocrit and percentage of HbS by quantitative electrophoresis.
HbS - hemoglobin S, PRBCs - packed red blood cells, U - unit

Complications of transfusion are many and can be grouped into infectious and non-infectious types. It is lengthy and beyond the scope of this review to detail each of these complications.

Transmission of infections. Transmission of infections is still a major concern following transfusion, and despite the increasingly efficient improvement in donor screening,[43] around 10% of adult sickle cell patients are hepatitis C positive, and 30% of them have significant liver damage.[44] Bacterial infections are also well known complications following BT.[45]

Alloimmunization. Alloimmunization is a significant and common problem following BT in patients with SCA, which lead to difficulties in compatibility testing and initiates life-threatening complications. The frequency of 18-47% of SCA patients having alloimmunization is thought to be an underestimation as a significant proportion of alloantibodies rapidly vanish or falling undetectable.[46-51] The relatively high prevalence of this phenomenon in patients with SCA could be explained by distorted immune response, genetic make up of these patients as well as transfusion load. One way of dealing with this problem is to transfuse phenotypically (E, C, Kell, and Fy^a) matched blood to chronically transfused patients. This will facilitate reducing and resolving the problem of alloimmunization.[52] This has to be early tackled with neonatal identification of SCD, which can significantly reduce mortality and morbidity, as well as preparing for further planning.[53] A further problem which arises with the progress we dropping in alloantibodies is the development of autoantibodies, which are non-hemolytic and can be recently identified due to increased sensitivity of reagents.[47]

Iron overload. Iron overload is a real risk in adults with SCD and considered a prognostic indicator of morbidity and mortality. Approximately 50% of patients with Hb SS who are admitted to the hospital receive BT, averaging 10 units of PRBCs per patient per year. This is equivalent to approximately 2gm of iron per patient per year **(Table 1).** Iron overload can be estimated by measurement of hepatic iron stores by chemical analysis of tissue obtained by liver biopsy, magnetic resonance imaging, computerized tomography, dual channel super-conductive quantum interference devise, serial measurements of serum ferritin, iron levels, and total iron binding capacity.

Techniques of blood transfusion. There are 2 ways for BT in SCD: the simple (additive) transfusion or the exchange transfusion, and the later can be achieved either manually or by erythrocytapheresis. Simple BT is most commonly used in those with symptomatic anemia from aplastic crisis, hemolysis, sequestration in spleen, liver or lungs, ACS, in multiorgan failure, and in the perioperative period.[53] Exchange BT on the other hand is used in situations where tissue oxygenation is crucial, and this can be achieved either manually **(Table 2)** or by erythrocytapheresis, which can be used by continuous flow cell separators, as it is efficient in minimizing iron load.[10,54-59] The most common indications for exchange BT include stroke, ACS, and multiorgan failure. This method can be carried out as an acute isolated event or on chronic programmed intervals in an attempt to prevent or treat complications like stroke or cardiopulmonary compromise.

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Abstract

Sickle cell disease (SCD) occurs frequently in the Saudi population and is often associated with high morbidity and disabilitating complications. The search for drugs to ameliorate the clinical presentation of SCD has been going on for the last 3 decades. **Aim:** The objective of this investigation was to study the effect of piracetam on the clinical presentation, hematological and relevant biochemical parameters in children of two different age groups suffering from severe SCD. **Study design:** A double-blind, placebo controlled, randomized multicentre trial conducted in different regions of Saudi Arabia. **Patients and methods:** Children (3-12 years) suffering from severe SCD as judged from severity index of 6 or more were enrolled in the study. One hundred and one children were included of whom 87 (79 SCA and 8SPO -thal) completed the one year treatment protocol. The drug/placebo was received from UCB Company in coded boxes and administered as intravenous infusion during crises (300 mg/kg/day) and orally 160 mg/kg/day) during follow-up period. The base line clinical data was recorded and hematological and biochemical parameters were assessed. The patients were treated and followed-up for a one year period and the follow-up was conducted every 8-12 weeks. On completion of the study period, the codes were decoded and the patients were grouped according to whether they had received piracetam or placebo and on the basis of age i.e. 3-6 years and 7-12 years of age. **Results:** The results were separately analyzed for the 3-6 and 7-12 years age groups. In terms of age, weight, height, SI, number of blood transfusions received and number of hospitalization both groups (i.e. placebo and piracetam) were statistically homogeneous. The results of the placebo and Piracetam treated groups were analyzed and a statistically significant decrease was observed in SI, number of crises, blood transfusion requirements and extent of hospitalization in the groups treated with piracetam compared to the placebo group. No differences were seen in the levels of hematological and biochemical parameters and Hb F level. **Conclusion:** Piracetam can be used for the amelioration of the clinical presentation of SCD. Even after discontinuation of the drug it's beneficial effects remain for several months.