Review: clinical transfusion management in sickle cell disease

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Sickle cell disease (SCD) is the most common genetic disorder in the United States, affecting individuals of sub-Saharan African, south Asian, and Mediterranean ancestry. The abnormality is a mutation in the sixth amino acid residue of the beta globin chain from glutamic acid to valine (β^s); resulting in a hemoglobin tetramer that may polymerize during normal oxygen carriage, causing the characteristic crescent or sickle-shaped RBCs in the peripheral blood for which the disorder is named. The abnormal RBCs are fragile, causing chronic hemolysis that results in anemia as well as a vasculopathy that causes ischemic damage to many body organs, including the spleen, kidneys, lung, and brain.

SCD includes a number of syndromes of variable frequency and severity. Sickle cell anemia (HbSS—homozygous for two β^s genes) is the most common, occurring in about 1 in 350 African American births.[1] Symptomatic double heterozygote states for hemoglobins that interact with β^s are less common and include sickle C disease (HbSC), and sickle beta thalassemia (HbS-thalassemia, with the designation β^o when no hemoglobin A is produced and β^+ when some A is present). While patients with HbSS experience the majority of the complications requiring RBC transfusion, such conditions are all experienced albeit less frequently by persons with other forms of SCD.

RBC transfusion, either to quickly increase the oxygen carrying capacity from acute exacerbation of anemia or to chronically suppress the production of β^s-containing RBCs, is a mainstay of treatment for SCD. Although stable compensated anemia, which patients with SCD have at baseline and during uncomplicated acute painful crisis, does not require transfusion, the majority of adult patients have required transfusion at least once in their lives. This article will review the commonly used transfusion methods, the indications for transfusion, and the current management of iron overload in patients with SCD.[1,2]

Red Blood Cell Product Selection and Methods of Administration

Immunologic considerations

Alloimmunization, as a result of antigenic discrepancy between patients of African ancestry and predominantly Caucasian blood donors, has historically affected 5 to 50 percent of patients with SCD. Previously undetected alloimmunization, a problem made worse by multiple sites of care and transfusion center ignorance of complete transfusion history, may increase the occurrence of delayed hemolytic transfusion reactions (DHTR). Further, the clinical signs of DHTR may mimic those of sickle cell crisis: pain, low-grade fever, and exaggerated anemia, so diagnosis may be further delayed.[1,2] Once such a hemolytic reaction begins, patients with SCD may undergo hemolysis of autologous as well as transfused RBCs, an autohemolysis-hyperhemolysis syndrome which may be persistent and severe.[3,4] During such events, further transfusion of even crossmatch-compatible RBCs should be avoided, if possible. The recommended treatment is usually corticosteroids and intravenous gamma globulin; erythropoietin is added if reticulocytopenia is present.[1]

Product selection

Because of the increased, lifelong need for RBC transfusion as well as the increased probability and consequences of alloantibody formation in persons with SCD, most centers that care for a large number of these patients perform extended RBC antigen typing before the first transfusion. RBC components, known to be phenotypically matched for ABO and Rh (Cc, D, Ee) and K can then be crossmatched. Theoretical calculations suggest that the use of a limited extended-phenotype matching for these antigens would prevent 53 percent of antibodies in SCD patients.[5] Extended-phenotype matching for ABO, Rh, and K has been shown in a multicenter trial to reduce the

alloimmunization rate in patients with SCD from 3 percent to 0.5 percent per unit transfused and to reduce DHTR by 90 percent.[6] While this is recommended, it may not be practical in all sites.[1] Further, since the majority of the units will be used in chronic transfusion programs described below, units less than 7 to 10 days old are selected for transfusion to SCD patients, whenever possible. Selected units should be screened and found to be hemoglobin S (HbS) negative.

In our center, we attempt to obtain an extended RBC phenotype on all HbSS and HbS-β^o thal patients at a routine clinic visit before their second birthday. The phenotype is stored in the blood center records as an "antibody" so that when a clinical order is received for RBCs, phenotype-matched RBCs can be provided. Our hospital blood bank maintains an inventory of several units of group O, D– (extended antigen phenotype known), K– units to be used for urgent transfusion of patients with SCD; more can be obtained from the regional blood center within 2 to 4 hours. When an extended phenotype has not been performed before the request for crossmatch, the clinician is given the option of awaiting limited antigen typing from the regional blood center that may take 8 to 12 hours or accepting crossmatch compatible group O, D–, K– units already on site. For chronically transfused patients, who use the majority of the extended-phenotyped units, the transfusion is scheduled with the blood bank in advance so additional units with the required phenotype may be moved to the hospital blood inventory the day before the planned outpatient use.

To ensure that sufficient extended-phenotype compatible RBCs are available, our sickle cell program has paired with the regional blood center to establish a Special Care Team: patients volunteer to tell their stories in donor recruitment literature branded with the logos of the team, the hospital, and the donor center. Volunteer donors are asked to self-identify as African American and to indicate that they are willing to be recalled for the program. RBC samples from identified donors are then extended-antigen typed and thereby linked to the program, not to a specific patient. Units collected under this program receive a special tag at the time of release for transfusion, raising awareness of the need for special donors and of the program. In the first 18 months of program operation, the donor center recorded a 3.3 percent increase in African American donors and a 7.6 percent increase in units donated.[7] Many other centers have established similar programs.

Transfusion Methods

Acute versus chronic transfusion

Acute transfusion is given for an urgent problem, usually accelerated anemia in SCD patients, and is the standard form of transfusion. Infusion of the bank RBCs raises the hemoglobin and restores circulating intravascular volume and oxygen carrying capacity. Although blood substitutes have been tried in patients with SCD during acute events, currently the short half-life of such products and concerns about repeated administration limit their usefulness.

Chronic or long-term transfusion is managed through a program in which patients receive RBCs every 3 to 6 weeks to suppress their own HbS production and to ameliorate intravascular sickling and further organ damage. Within 1 to 3 planned monthly transfusions, the reticulocyte count is usually suppressed to less than 5 percent, the goal being to maintain a patient at a desired hemoglobin level and below a specific percentage of HbS indefinitely with continued transfusion.

Chronic transfusion—simple versus exchange

The usual volume for simple transfusion is 2 to 3 units for an adult and 10 to 15 ml/kg for a pediatric patient, administered by peripheral or central venous access over 4 hours. Such volumes are the easiest to administer and reduce the concentration of HbS by dilution. If the patient is particularly anemic (below 5–6 gm/dL) it may be possible to decrease the percentage of HbS to below 30 percent with serial, simple transfusions. However care must be taken to prevent volume overload particularly if more than one transfusion is planned in a short period of time. Similarly, it is important to avoid a Hb of more than 11 gm/dL and its attendant hyperviscosity, which may precipitate a painful crisis or stroke, unless the percentage of HbS is less than 30 percent.[1]

Exchange transfusion can be performed manually or by mechanical erythrocytapheresis. In acute situations, exchange transfusion can rapidly decrease the percentage of HbS while maintaining euvolemia and avoiding hyperviscosity. Chronic exchange transfusion, which usually requires two good sites of intravenous access, can maintain the benefits of low HbS percentage while avoiding iron overload.[8] If isovolemic hemodilution methods are used, transfusional iron burden may even be reduced by subsequent procedures.[9]

Alternatives to Transfusion—Hydroxyurea

Hydroxyurea therapy reduces the frequency of painful events and acute chest syndrome episodes in patients of all ages with SCD. It also has a clear benefit on increasing survival.[10] Similar results have been seen in pediatric patients with minimal toxicities, most commonly reversible myelosuppression. This chemotherapy agent is well tolerated orally, but does require at least monthly monitoring of the blood count and evaluation of other potential toxicities such as gastrointestinal upset, splenic enlargement and blood chemistry abnormalities. This requirement for frequent monitoring in addition to the theoretical risk of teratogenicity and leukemogenicity have limited hydroxyurea's acceptance by many patients.

Indications for Transfusion

Central nervous system

1. Secondary prevention of thrombotic stroke

Acute infarctive stroke is the most common neurologic disorder in patients with SCD, occurring in 7 to 10 percent of HbSS patients during childhood.[11] These events occur as the result of a progressive intracranial vasculopathy caused by sickle cell induced damage to the endothelium. Chronic RBC transfusion is the gold standard in the prevention of recurrent events, having been reported to reduce the rate of these events from 47 to 93 percent to 10 to 20 percent.[12] However, transfusions must be continued lifelong as discontinuation is well documented to result in 50 percent recurrence of ischemic central nervous system (CNS) events up to 12 years later.[13] Initially the intent is to transfuse to maintain a pretransfusion Hb of 9 to 10 gm/dL, HbS less than 30 percent, and reticulocyte count less than 5 percent. After four years of continuous transfusion without recurrent neurologic events, some centers change the pretransfusion goal to a Hb of 8 to 8.5 gm/dL and a HbS of less than 50 percent to decrease transfused iron and lengthen the interval between transfusions.[14] Intracranial hemorrhage is also seen in up to 25 percent of adult patients, but the utility of chronic transfusion in secondary prevention of hemorrhagic stroke is less well established.[1]

In a single-institution trial, Ware reported that patients on chronic transfusion for secondary stroke prevention can overlap treatment with concomitant hydroxyurea therapy while gradually reducing the intensity of transfusion and still maintain protection

again recurrent CNS events.[12] Once they are stable on hydroxyurea, phlebotomy can then be used to resolve the transfusional iron overload. The currently enrolling NIH-NHLBI-funded Stroke with Transfusions Changing to Hydroxyurea (SWiTCH) study is designed to test this approach in a multicenter setting. At this time, however, the use of hydroxyurea to prevent primary or recurrent CNS events must be considered investigational.

2. Primary prevention of stroke

With the high-occurrence risk of stroke in children with HbSS, a great deal of interest has been focused on prediction of which children are at risk. Risk factors for thrombotic stroke identified in the Cooperative Study of Sickle Cell Disease include a prior transient ischemic event, low steady-state Hb, elevated systolic blood pressure as well as recent frequency of acute chest syndrome.[11] The Stroke Prevention in Sickle Cell Anemia (STOP I) trial demonstrated that, in children aged 2 to 16 years with a time average mean velocity of more than 200 m/s on transcranial Doppler study, chronic transfusion could decrease the risk of initial stroke by 90 percent.[15] In the subsequent STOP II study, it could not be defined when it was safe to stop transfusions, reinforcing the recommendation that they continue indefinitely for both the primary and secondary prevention of stroke.[1]

Multiorgan failure syndrome

In this life-threatening complication, which transpires during a severe painful crisis, generalized vaso-occlusion occurs, resulting in a rapid fall in Hb and platelet counts, encephalopathy, and evidence of renal and hepatic dysfunction. Prompt exchange transfusion to a HbS less than 30 percent and a Hb of about 10 gm/dL has been associated with improved survival and recovery of organ function.[1,2]

Acute chest syndrome and pulmonary hypertension

Acute chest syndrome is a unique pulmonary event in patients with SCD defined as a new lobar or segmental infiltrate on chest radiograph, with fever, hypoxia, and respiratory symptoms, and is frequently associated with an acute decline in Hb of 2 gm/dL or more. Acute chest syndrome is the leading cause of death of patients with SCD and recurrent events have been implicated in the development of pulmonary hypertension. There are no direct data that simple transfusion can hasten the resolution of acute chest

syndrome.[1,2] Most clinicians advise simple transfusion if there is a significant supplemental oxygen requirement and the Hb is below 7 to 8 gm/dL. Exchange transfusion is reserved for patients with rapidly progressive courses, those in whom adequate oxygenation cannot be maintained on 50 percent supplemental oxygen, and others who might experience dramatic improvement during the procedure.[2,9]

During the STOP I trial, data accumulated that compliance with chronic transfusion reduced the incidence of acute chest syndrome in pediatric patients from 15.7 to 2.2 events per 100 person years (p=.0001).[16] Clinicians will often advise a short term (6 months or less) of chronic transfusion therapy for patients with unusually severe or frequently recurrent acute chest syndrome. Treatment with hydroxyurea is also appropriate, following or instead of the short term chronic transfusion program for prevention of recurrent acute chest syndrome.

About one-third of adults with HbSS are reported to have pulmonary hypertension, defined by a tricuspid regurgitant jet velocity of equal to or more than 2.5 m/s, a diagnosis associated with premature mortality. Chronic transfusion has also been proposed as a treatment to stop the progression of or reverse early pulmonary hypertension in small pilot studies. However, the true role for chronic transfusion in management of patients with pulmonary hypertension may depend, as in primary stroke prevention, on screening for early risk groups.[1]

Pain

There are no data that transfusion can hasten the resolution of a painful event once it has started. However, the STOP trial did confirm that aggressive chronic transfusion can reduce the frequency of painful events from 27.1 to 9.7 events per 100 patient-years (p=.014).[16] Again clinicians frequently offer a short-term chronic transfusion program for recurrent painful events; however hydroxyurea has also been demonstrated to reduce the frequency of this complication.

Exaggerated acute anemia

During the course of many complications of SCD, patients may become more anemic than is usual for them. RBC transfusion is indicated when there is evidence of tissue hypoxia or end-organ stress. The most common cause of acute anemia is transient RBC aplasia caused by human parvovirus B19. This virus induces RBC production arrest for 4 to 14 days, half of the RBC life span in some forms of SCD. The Hb falls and the reticulocyte count is usually below 1 percent. RBC transfusion to attain a Hb of 8 to 9 gm/dL is indicated and close follow-up required until the reticulocyte count returns to normal.

Acute splenic sequestration and hepatic sequestration

HbS-contained RBCs may become trapped in the small vessels and sinusoids of the spleen and liver, resulting in rapid organ enlargement and dysfunction. Patients present with anemia and pain over the enlarged organ, and thrombocytopenia is frequently seen in severe events. Acute splenic sequestration is most common in children with HbSS and HbS-β° thal between 6 months and 5 years of age, where it can be rapidly fatal if not promptly diagnosed and managed. RBC transfusions both reverse the symptoms of acute anemia and promote release of the sequestered cells. Care must be exercised to prevent over-transfusion and a rise in Hb to more than 11 gm/dL, at which point the patient is at risk for hyperviscosity and sludging, particularly within the intracranial vessels.

Chronic, sometimes painful, splenomegaly, which can be seen in patients with all forms of SCD but particularly in adolescents and young adults with HbSC, may also be observed. This does not usually require acute transfusion but may place the patient at increased risk of exaggerated acute anemia during intercurrent illness. For recurrent splenic sequestration episodes requiring transfusion, splenectomy should be considered. A short-term chronic transfusion program may be used to foster involution of the spleen or temporize until the clinician or the family is comfortable with splenectomy.

Hepatic sequestration is marked by a 3- to 4-fold increase in transaminases and bilirubin in association with anemia and painful hepatomegaly. Acute transfusion is required when anemia is severe and over-transfusion should be avoided as outlined above.

Priapism

Priapism, a prolonged painful erection of the penis, is a very common complication of SCD, occurring most commonly in patients with HbSS beginning at 2 to 3 years of age. Although anecdotal response to RBC therapy has been reported, there has never been a randomized controlled trial of simple or exchange

transfusion in management of either prolonged or recurrent priapism. Recent research has demonstrated the frequent success of alternative medical and surgical strategies to relieve the acute prolonged (more than 4-hour) episodes of priapism that may lead to penile ischemia, fibrosis, and impotence.[17] Further, an association between SCD, priapism, exchange transfusion, and neurologic events dubbed the ASPEN syndrome has been reported.[18] As a result, most centers reserve transfusion for single episodes unresponsive to alternative management that have persisted for more than 24 hours. Limited chronic RBC transfusion has also been used to prevent recurrent priapism in patients with frequently recurrent prolonged episodes.

Pregnancy

There are conflicting data regarding the benefit of regular "chronic" transfusion during pregnancy. Instead most centers provide selective transfusion targeted to address clearly identifiable medical and obstetric complications such as hypoxemia, progressive symptomatic anemia, acute chest syndrome, splenic sequestration, or pre-eclampsia during pregnancy.[1,2]

Leg ulcers

Leg ulcers occur on either side of the malleolus spontaneously or following minor trauma, often becoming infected, and are very slow to heal. While higher Hb levels are thought to benefit wound healing, there is a paucity of clinical data to support use of chronic transfusion in SCD-related leg ulcers.[1,2]

Preparation for general anesthesia

The need for surgical intervention is common in patients with SCD and general anesthesia is associated with painful crisis, acute chest syndrome, and excess mortality within the week. Routine preoperative and often exchange transfusions have been the standard practice for patients undergoing major surgery, particularly where upper abdominal incisions may predispose to hypoventilation, but the practice is based on little firm data.

The preoperative transfusion study found no difference in outcome between routine preoperative transfusion to about 10 gm/dL by aggressive exchange to less than 30 percent HbS and simple transfusion to the target Hb regardless of HbS percentage. However the simple transfusion group had the advantage of reduced transfusion-related complications.[19] In addition, this trial was limited by enrollment of few

patients more than 21 years of age with known cardiopulmonary dysfunction (recurrent acute chest syndrome or pulmonary hypertension) so some authors continue to advocate exchange transfusion for selected high-risk patients.[1] Other authors have demonstrated that for low-risk cases transfusion is not required.[20] Thus the decision to transfuse must be individualized. In our center, patients with SCD with a steady-state Hb less than 8.5 gm/dL (hemoglobinopathies other than HbSS and HbS-β^o thal), not undergoing upper abdominal surgery (any case other than cholecystectomy and splenectomy), and without a history of recent or recurrent acute chest syndrome would be less likely to require preoperative transfusion.

Iron overload

The obligate burden of recurrent acute or chronic transfusion is iron overload. Before 2006, iron overload necessitated chelation with subcutaneous or intravenous deferoxamine (Desferal, Novartis Pharmaceuticals Corp., East Hanover, NJ). The rigorous demands of subcutaneous deferoxamine infusion, 10 to 12 hours a night, 5 or 6 nights a week, invited poor adherence, leaving patients protected from the complications of SCD but at risk for hepatic and cardiac damage from the transfused iron.

The oral iron-chelator deferasirox (Exjade, Novartis Pharmaceuticals Corp.) was just licensed in the United States for treatment of transfusional hemosiderosis in patients 2 years of age and older. This oral dispersible tablet is taken on an empty stomach 30 minutes before eating daily and causes chelated iron to be excreted in the stool. In head-to-head studies iron excretion equivalent to the iron removed with deferoxamine was observed. Deferasirox has a significant side effect profile with pruritic rash, abdominal pain, and elevations in both creatinine and transaminases being seen in 6 to 38 percent of patients. Most toxicities respond to suspension of the medication and reintroduction at a lower dose.[21] While there are other oral iron-chelators in advanced clinical trials, deferasirox is the only one approved for use in the United States.

The availability of this oral iron-chelator will likely increase the willingness of clinicians to use RBC transfusion therapy. However, the efficacy of this medication to remove all concerns of iron overload from patients with SCD who require chronic or repetitive transfusion has not yet been demonstrated

and given the significant side effects observed in the licensure trials and in early clinical use, significant concerns still exist.

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