Transfusion Support in Sickle Cell Anemia

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INTRODUCTION

Sickle cell anemia affects about 32,000 to 50,000 patients in the United States. This Update briefly reviews sickle cell disease (SCD) and discusses aspects of red cell transfusion in its management.

BACKGROUND

8 to10% of the African-American population is heterozygous for the hemoglobin S gene, usually also possessing a gene for normal hemoglobin A1. Roughly 40% of the hemoglobin of "sickle trait" carriers consists of HbS. These individuals are usually asymptomatic, and have normal life expectancies. 1 in 650 African-Americans is homozygous for HbS and has SCD.

The mutation is a single base-pair substitution of adenine for thymine in the beta globin gene on chromosome 11. This deceptively small change codes for valine instead of glutamic acid at amino acid position 6 in the hemoglobin beta chain. The resulting hydrophobic region on the deoxygenated HbS molecule binds reversibly to corresponding regions on adjacent HbS molecules, causing lateral aggregation into long, rod-like polymers. Within red cells, dehydration concentrates polymerized sickle hemoglobin into elongated trapezoidal crystals which distort RBCs into the characteristic sickle shape. Membrane distortion is initially reversible with hydration and oxygenation, but "sickling" eventually becomes permanent, displaying a remarkable array of pathology. Ion transport channel dysfunction allows influx of calcium and escape of potassium, chloride and water, worsening dehydration. Denatured HbS promotes iron-mediated oxidative damage, rendering the normally pliable membrane rigid, fragile, and subject to removal by splenic macrophages. Sickled membranes present novel antigenic sites which bind IgG, encouraging phagocytosis. Sickle cells are prone to entanglement and abnormal interactions with endothelium and clotting factors, promoting vascular occlusion.

PATHOPHYSIOLOGY OF SCD

The clinical spectrum of SCD is broad. Disease severity varies greatly with other genetic factors, co-morbidities and the complications of the disease itself; e.g., sickle-related strokes tend to recur. Patients with high percentages of fetal hemoglobin (HbF) persisting beyond infancy (naturally or via hydroxyurea therapy tend to have less severe disease. Other abnormal hemoglobins (e.g., HbC) also modulate SCD.

The major features of SCD include chronic hemolytic anemia, vaso-occlusive crises in various tissues, progressive infarction leading to chronic pain, deformity, and organ failure; sequestration crises in lung, spleen, liver, and mesentery; and aplastic crises due to human parvovirus B19 infections. Splenic infarction leads to functional asplenia early in life, with increased risk of overwhelming sepsis (particularly with *Streptococcus pneumoniae*). Common major complications include priapism, thrombotic stroke, and acute chest syndrome (caused by pulmonary vaso-occlusion/sequestration and/or marrow infarction leading to systemic fat embolization syndrome). Chronic anemia and ineffective erythropoiesis cause marrow expansion and characteristic bony abnormalities, hepato-splenomegaly due to extra-medullary hematopoiesis, and increased iron absorption. Iron overload is aggravated by transfusion.

TRANSFUSION THERAPY

Simple PRBC transfusion and red cell exchange (RCE) are important therapies for SCD. Reducing the percentage of HbS prevents or reverses intravascular sickling. Sickled red cells are not only short-lived and dysfunctional but inherently harmful, and patients frequently benefit from exchange with normal donor red cells. Treatment should be tailored to the situation.

Many SCD patients who are relatively asymptomatic do not need transfusion as long as they are adequately hydrated and oxygenated with stable hematocrits between 25 and 30%. Uncomplicated pain crises can be managed with fluids, oxygen, and analgesics; transfusion adds little benefit acutely. For SCD patients with no history of serious complications, the drawbacks of prophylactic transfusion (alloantibody formation, transfusion-transmitted infection, and iron overload) outweigh any advantages.[1,2] In addition, transfusion suppresses endogenous erythropoiesis, posing the risk of profound anemia if transfused red cells (and even native red cells) undergo brisk hemolysis due to allo-(and/or auto-) antibodies.

Episodic simple transfusion is indicated for symptomatic anemia due to hemolysis, sequestration, bleeding, or aplastic crisis, and should aim for a hematocrit not greater than 35% to avoid hyperviscosity. Achieving a hemoglobin of 10g/dL prior to surgery may be as effective as RCE in preventing complications.[3]

Simple red cell transfusion to a hemoglobin of 10 g/dL is appropriate in the initial management of stroke, acute chest syndrome, and priapism, particularly when the patient's baseline hemoglobin is substantially lower, and/or exchange transfusion is unavailable. Simple transfusion requires fewer PRBC units and no special expertise, and may be followed by RCE in patients who do not improve sufficiently.

RCE is indicated for severe sickle crises in patients with higher hemoglobin levels in whom simple transfusion increases viscosity without substantially reducing the percentage of HbS. RCE is typically accomplished via erythrocytapheresis. (Manual exchange is an alternative for patients who can tolerate the volume and hemoglobin shifts.) A one-volume exchange in an adult requires 6 to 8 units of PRBCs (50-60 mL/kg in children), reducing the proportion of HbS below 30%. Erythrocytapheresis has the drawbacks of complexity, expense, and frequent need for central venous access, especially in smaller patients. However, RCE helps avoid iron overload, a serious complication of chronic transfusion.

SCD patients suffering stroke and acute chest syndrome may require scheduled prophylactic transfusion to prevent recurrences. Children with abnormal trans-cranial Doppler studies can be treated to prevent first strokes.[4] Some patients with unusually frequent pain crises benefit from chronic transfusion. Guided by measurement of HbS, the treatment interval (3 to 5 weeks) and number of units transfused can be adjusted as needed. Typical scheduled RCE targets are a post-exchange HbS level below 30%, and a pre-exchange level below 50%. Prophylactic transfusion of either type reduces the risk of recurrent stroke from over 60% to less than 10%, but, once begun, treatment must be continued indefinitely, or the risk of stroke returns.[5]

BLOOD PRODUCT CONSIDERATIONS

Due to frequent transfusion and the antigenic differences between (mostly African-American) SCD patients and (mostly Caucasian) blood donors, alloimmunization to multiple red cell antigens (especially C, E, K, Kidd, and Duffy) occurs in at least 18% of SCD patients.[6] Initial pre-transfusion antigen phenotyping of the patient helps identify compatible units. Whenever possible, units from African-American donors as well as K-, C-, and E-antigen negative units should be used.

Alloimmunization to high incidence antigens is common, and compatible units may be available only from family members or rare donor registries. If transfusion cannot be delayed, it may be necessary to give incompatible units. Resulting immune-mediated hemolysis may

resemble sickle-related hemolysis; a direct Coombs test helps to distinguish them.

Most institutions provide sickle-negative, leuko-reduced PRBC units to their SCD patients. Sickle-negative RBCs better dilute circulating HbS; screening units with a hemoglobin solubility test is sufficient. Leuko-reduction helps avoid HLA sensitization, platelet alloimmunization, and febrile non-hemolytic transfusion reactions. The latter can mimic more serious transfusion reactions, forcing the discontinuation of needed transfusions and wasting carefully matched, rare blood products.

THE FUTURE

Stem cell transplantation offers some hope to severely affected younger patients with HLA-matched donors. Experience with transplant for non-malignant blood disease is limited. Technical questions, socio-economic barriers, and patient distrust of these therapies limit their application in SCD. Other potential avenues include gene replacement and manipulation of other genes (e.g., HbF, HbA2, thalassemia genes) which modulate the effects of sickle cell anemia.

For now, careful disease management with judicious use of transfusion is the best strategy for most patients.

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