TITLE: Methods to Screen for Hemoglobin S in Blood Donors Selected for Exchange Transfusions: A Review of the Clinical Effectiveness and Guidelines

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CONTEXT AND POLICY ISSUES:

Hemoglobin (Hb), a protein in red blood cells (RBC), carries oxygen from the lungs to the rest of the body. Hemoglobin S (HbS), a structural variant resulting from a mutation, causes RBCs to deform into a sickle shape whenever oxygen levels are low. Sickled RBCs stick together and block blood flow through small vessels, causing pain and reducing oxygen capacity.[1] When one sickle beta-globin gene is inherited along with a normal beta-globin gene, HbS is inherited in heterozygous form (HbAS) as sickle cell trait (SCT). The carrier condition is benign because the normal form of the gene produces 55% of the body's Hb.[2] When two sickle beta-globin genes are inherited, HbS is inherited in homozygous form (HbSS) as sickle cell disease (SCD).[2] HbS can also be inherited with HbC (HbSC) or beta thalassemia (HbS-beta thalassemia) to produce SCD.[1] RBCs of HbSS individuals contain 90% HbS.[2] SCD results in sickle cell anemia and clinical complications including stroke, aseptic bone necrosis, serious infections, renal failure, neurological deficits, and delayed growth.[3]

According to the 2001 Canadian census, over 3.7 million Canadians (12.5% of the population) identified their ethnic origin as one known to be at increased risk of thalassemia or hemoglobinopathy.[4]

In the United States, more than 15 million RBC units are collected annually for transfusion to approximately 5 million patients.[2,5] Blood donors and recipients undergo extensive testing prior to transfusion to limit serious complications but donors are not screened for SCT.[2] In the United States, blood donors with hemoglobinopathies are acceptable donors unless they have SCD (HbSS) or anemia.[5] As many as 100,000 donations each year contain HbS based on a 0.8% prevalence of HbAS in United States blood donors.[2] Post donation testing for HbS is done on a limited number of units to provide HbS-free units for transfusion to SCD patients and leukoreducible units because SCT causes filtration failure.[5] HbS variants are confirmed by a variety of methods including HbS solubility test, sodium metbisulfite test, high-performance liquid chromatography (HPLC), isoelectric focusing (IEF) and Hb electrophoresis.[5,6] Genetic

testing for mutations in the beta-globin gene can confirm a diagnosis of SCD. Ontario is one of the first Canadian provinces to establish newborn screening for SCD (www.newborncreening.on.ca) but most blood donors are unaware of their status.[2] Transfusion-induced hemoglobinopathies can occur when a patient receives a transfusion of abnormal Hb.[5] This issue is most relevant in infants undergoing exchange transfusion. While leukodepletion filters are used across Canada, blood donated for transfusion to newborn infants is not routinely screened for HbS.[7]

RESEARCH QUESTIONS:

1. What is the clinical effectiveness of methods used to screen for hemoglobin S in blood donors selected for exchange transfusion?

2. What are the guidelines regarding screening for hemoglobin S in blood donors selected for exchange transfusion?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 6, 2010), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between January 1 2000 and June 30 2010. No filters were applied to limit the retrieval by study type.

SUMMARY OF FINDINGS:

Two relevant evidence-based guidelines were identified that provided guidance regarding screening for HbS in donors selected for exchange transfusion.[8,9] Four additional review articles,[2,10-12] two non-randomized studies,[5,13] and one guideline[7] of potential interest are included in the appendix.

Guidelines and recommendations

The New York State Council on Human Blood and Transfusion Services produced guidelines for transfusion therapy of infants in 2004.[8] While a list of general references and committee members are listed, no methods were provided regarding how the evidence was graded or how the guideline was formulated. The guidelines for exchange transfusions recommend that fresh (up to 7 day old), irradiated, HbS-negative and CMV-seronegative or leukoreduced RBCs be reconstituted with fresh frozen plasma or albumin for exchange transfusion.[8] No strength of recommendation was given.

The British Committee for Standards in Hematology published a Guideline for the Administration of Blood Products regarding the Transfusion of Infants and Neonates in 2004.[9] While a list of general references and committee members are listed, no methods were provided regarding how the evidence was graded or how the guideline was formulated. This guideline recommends that patients with thalassaemia and SCD be extensively phenotyped for RBC antigens before transfusion [Level IIb evidence, grade B recommendation]. RBC preparations

for thalassaemia and SCD should be tested for HbS prior to transfusion, as SCT positive RBCs should not be transfused [Level IIb evidence, grade B recommendation].[9] Levels of evidence and grades of recommendation were not defined within the guideline.

Limitations

No systematic reviews, meta-analyses, or randomized controlled trials were identified from the literature search to address the question of clinical effectiveness of methods used to screen for hemoglobin S in blood donors selected for exchange transfusion. The evidence identified for this review and included in the appendix is limited in that it does not fully answer the questions regarding the clinical effectiveness of techniques to screen donated blood for HbS.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

New York and British guidelines recommend HbS-negative blood be used for exchange transfusion in infants. No conclusions can be made about the clinical effectiveness of methods used to screen for HbS in blood donors selected for exchange transfusion, as no relevant evidence was identified to answer this question.

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APPENDIX: Summaries of Additional Articles of Potential Interest

Non-Randomized Studies

Two clinical laboratories in New York investigated the occurrence of transfusion-induced hemoglobinopthies as part of departmental quality improvement.[5] HPLC is used to identify and quantify Hb variants because of its high throughput, superior resolution, and improved precision compared to Hb electrophoresis.[5] Using HPLC, Hbs are identified by retention times, percentages, and shapes of the corresponding peaks in the chromatograms. The diagnosis of a hemoglobinopathy can require a review of the patient's medical and laboratory records as well as matching the abnormal peaks characteristics with known examples in an instrument manufacturer's variant library of abnormal Hb.[5] The labs used Hb HPLC (Bio-Rad VARIANT II and the corresponding Beta-Thalassemia Short Program, Hercules, Calif) or Hb electrophoresis (Beckman Coulter Paragon Electrophoresis System, Fullerton, Calif) to characterize all patient specimens for Hb identification and quantification. A transfusion-induced hemoglobinopathy was defined when a Hb variant was discovered in a recipient following the transfusion of a unit of blood containing abnormal Hb. While the overall number of specimens is not reported, the labs detected 52 incidences of hemoglobinopathies in 32 recipients caused by blood transfusion, of which 46 were HbC, 4 HbS, and 2 were HbO-Arab.[5] The percentage of abnormal Hb in the recipients ranged from 1.1% to 14% (mean, 6.5%) for HbC; 1.4% to 7.1% (mean 4.3%) for HbS; and 0.8% to 3.4% (mean 1.7%) for HbO-Arab. Multiple transfusions with abnormal Hb occurred in 11 patients with 2 patients receiving HbC and later S, and another patient receiving C and later O-Arab.[5] The authors concluded that hemoglobinopathies caused by blood transfusions are more common than previously reported. Diagnosis is challenging and can lead to misdiagnosis, unnecessary testing, treatment and counseling, according to the study's authors. If hemoglobinopathy from a unit of transfused blood is identified in a recipient, donors should be notified.[5]

A university hospital in Riyadh, Saudi Arabi studied the prevalence of SCT among blood donors and reviewed the benefits and risks of using SCT blood for transfusions.[13] The cross-sectional study was conducted on 1150 blood samples from donors attending King Khalid University Hospital from April 2006 to May 2006.[13] Blood samples were tested for HbS using solubility test, alkaline gel electrophoresis and glucose-6-phosphate dehydrogenase (G6PD)-deficiency by fluorescent spot test. Out of 1150 donors, 23 (2%) were diagnosed for SCT, 9 (0.78%) for G6PD deficiency and 4 (0.35%) for both conditions. The prevalence of SCT and 6GD deficiency was higher in donor blood than in the general population of Riyadh. Transfusion with G6PD-deficient blood carries the risk of hemolytic complications, especially if it is used for exchanged blood transfusion in neonates. Blood donated by individuals with SCT results in white blood cell (WBC) filtration failure and cannot be used to transfuse SCD patients. The authors recommend screening all units for SCT and G6PD deficiency and to defer donations from donors with either condition unless they are needed for special blood group compatibility, platelet apheresis or if they are likely to effect blood bank inventory.[13] The authors recommend that blood banks with limited resources where screening for SCT and G6PD is not feasible should screen units that are likely to be transfused to high-risk recipients, particularly if a single-unit transfusion is going to be undertaken.[13] SCT units should be labeled and stored in bags that allow increased oxygen saturation, according to the study's authors.[13]

Guidelines

The Canadian Pediatric Society revised guidelines for RBC transfusions in newborn infants in 2009.[7] The clinical practice guideline was prepared by the Genetics Committee of the Society of Obstetricians and Gynecologists of Canada and the Prenatal Diagnosis Committee of the Canadian College of Medical Geneticists. No method is provided regarding how the guideline was formulated. The guideline specifies that each unit of donated blood be analyzed for the presence of antibody to HIV-1, HIV-2, hepatitis C, human T-lymphotrophic virus, hepatitis B, surface antigen and HIV-I 24 antigen. Blood should be screened for syphilis and cytomegalovirus. High efficiency leukodepletion filters are used routinely across Canada.[7]

Review Articles

Safety issues related to transfusing blood from SCT donors was discussed in a review article in 2006.[11] In most countries, individuals with SCT are eligible for blood donation and 35% to 45% of their total Hb is HbS.[11] There is no standard practice regarding the screening of donors or the use of SCT RBCs for transfusion. Each blood centre develops its own regulation. Since the implementation of universal leukoreduction in several countries, problems associated with leukocyte filtration of SCT blood have been noted. RBC components from SCT donors often occlude WBC reduction filters. They don't filter completely, leading to a higher number of post filtration residual leucocytes. The major cause of filtration failure is polymeriztion of the HbS. SCT RBCs become rigid during storage suggesting that HbS may compromise the cells' elasticity. Blood units are not routinely screened for HbS and transfusion in some patients can result in anaphylactic haemoglobinuric reaction. Massive intravascular sickling has been reported after using SCT blood for exchange transfusions, and renal and splenic infarctions have been described in neonates.[11] The use of SCT RBCs for transfusion is usually prohibited in newborns or exchange transfusions in newborns.[11] The United Kingdom encourages blood donation from ethnic minorities but discards units if they block the filter. The authors recommend destroying all blood packets when HbAS is present or to use these RBCs only for use in adult SCD negative recipients requiring transfusion of RBCs of a rare or specific phenotype.[11]

A discussion of different approaches to screening blood units for SCT was presented in a review article from 2004.[2] Most blood banks screen RBC units for HbS before using the units for a neonate, for an intrauterine transfusion, or for a RBC or whole blood exchange transfusion.[2] While it may not be cost-effective to screen all blood donation units for SCT by hemoglobin electrophoresis based on low prevalence of SCT and limited number high-risk recipients, other methods of screening have been considered. Measurement of filtration time of RBC units may be a means of predicting HbS positivity in areas with a high prevalence of SCT donors.[2]

Unresolved issues associated with the leukoreduction of SCT blood were discussed in a review article in 2001.[12] SCT RBCs are not considered equivalent to non SCT RBCs and should not be given to patients whose blood oxygen might be compromised.[12] Leukoredution should be performed only on plasma and platelet components. If filtration of SCT red cell components is needed for rare blood groups, there is a better chance of obtaining successful leukoreduction filtration by filtration at cold temperatures possibly lowering the pH of the suspension media due to the nature of HbS solubility. There is no consensus on whether all donors or only donors whose ethnic origin may correlate with high prevalence of SCT should be screened for HbS. In

areas with low prevalence for SCT, it may be useful to screen units where the donors ethnic background implies a higher prevalence of SCT, units that fail to leukoreduce and units with prolonged filtration time. The use of SCT RBCs for transfusion purposes is usually prohibited in newborns or for exchange transfusions in newborns.[12]

A 2001 hematology review discussed advances in the care of sick and premature infants and increased use of blood transfusion therapy. Exchange transfusions are used to correct anemia, remove bilirubin, remove antibodies and replace RBCs. Ideally, plasma reduced cells are used that are not older than 5 days. The procedure involves an incremental removal of the patient's blood and replacement with fresh donor blood or plasma. The advantage of fresh cells is that hyperkalemia is avoided with good post transfusion survival and acceptable red cell oxygen affinity. However, units must be screened for SCD and G6PD deficiency.[10]