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Red Blood Cell Alloimmunization in Sickle Cell Disease: Prevalence in 2010

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Abstract

BACKGROUND—Transfusion of red blood cells is frequently required for care of individuals with sickle cell disease. Alloimmunization rates are high, and may be reduced by matching for red cell antigens that can cause alloimmunization.

STUDY DESIGN AND METHODS—During the PROACTIVE Feasibility Study, patients with sickle cell disease age two years or older admitted for pain without acute chest syndrome were enrolled for possible randomization to preventive blood transfusion or standard care. Transfusion and antibody histories were obtained at each site, and antibody screening was done, to assess transfusion burden and alloimmunization prevalence. Participating sites were surveyed regarding antigen matching practice.

RESULTS—237 patients (169 SS, 42 SC, 15 S β^0 -thalassemia, 11 S β^+ -thalassemia), 118 males and 119 females, were enrolled. Mean age was 19.3 years (range 2.0–68.0); there were 122 children and 115 adults. 75.8% had received at least a single transfusion of red blood cells prior to the study. Thirty-four patients (14.4%) had a history of at least one alloantibody and 17 of these had more than one. When surveyed, 19 sites (83% of responders) reported antigen matching to at least include C, E and K for transfusion of all patients with sickle cell disease.

CONCLUSION—Though antigen typing prior to transfusion of people with sickle cell disease and providing antigen negative units is now widely employed by sickle cell centers, the

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alloimmunization rate remains quite high in contemporary sickle cell populations and may be due in large part to transfusions received at institutions not providing extended matching.

Keywords

Transfusion; PROACTIVE; Duffy blood group; Cooperative Study of Sickle Cell Disease

INTRODUCTION

Transfusion of red blood cells is used to treat and prevent complications of sickle cell disease (SCD). Alloimmunization to non-ABO red cell antigens is potentially problematic^{1,2} and commonly encountered, at least in part due to antigen disparity between blood donors and people with SCD.³⁻⁵ Antigen-matching beyond standard ABO and Rh typing has reduced this alloimmunization rate in single institutional trials⁶⁻⁸ and in a research setting.⁹ In the PROACTIVE Feasibility Study (ClinicalTrials.gov NCT00951808),¹⁰ eligible patients with SCD hospitalized for pain were randomized to prophylactic transfusion to pre-empt nosocomial acute chest syndrome (ACS) or to standard care. Data collected included each patient's previously identified red cell alloantibodies. In addition, patients were screened for alloantibodies on enrollment to help assess feasibility of finding compatible red cells in a timely fashion for transfusion of randomized patients. These data inform regarding contemporary prevalence of alloimmunization in a broad group of patients with SCD cared for at 26 centers participating in the Sickle Cell Disease Clinical Research Network (SCDCRN), as compared to rates seen in participants in the Cooperative Study of Sickle Cell Disease (CSSCD) nearly three decades ago.¹¹

MATERIALS AND METHODS

PROACTIVE Feasibility Study Design

Thirty-one centers participating in the SCDCRN were encouraged to enroll patients in the PROACTIVE Feasibility Study, designed with an observation arm to determine the utility of elevated serum levels of secretory phospholipase A2 (sPLA2) in predicting ACS, and an intervention arm to evaluate the feasibility of using timely transfusion to prevent ACS in those at risk; type IIa sPLA2 is a calcium dependent protein that cleaves phospholipids to generate non-esterified fatty acids and lysophospholipids and is a potent inflammatory mediator. Subjects who developed fever and a serum level of sPLA2 > 100 ng/mL were eligible to be randomized to transfusion or standard care alone to determine whether ACS could be prevented. Patients with SCD, genotype Hb SS, SC, or β -thalassemia age 2 years or older admitted for pain who did not already have ACS were eligible for the observation arm of the trial. Exclusion criteria included: transfusion within 60 days of study entry or treatment with corticosteroids; coexisting conditions; and pregnancy or preferences/conditions (including a history of alloimmunization) that might require or preclude prompt transfusion.¹⁰

Site Survey Regarding Antigen Matching for Transfusion

Prior to commencement of PROACTIVE, participating centers were asked whether "extended phenotyping is routinely done on SCD patients". After termination of the study,

sites were again polled as to whether patients with SCD (or a subgroup, i.e. Hb SS or chronic transfusion patients) who need red blood cell transfusion are given red blood cells not only matched for ABO/Rh and any previously identified alloantibodies, but also matched for additional antigens. If so, a check-off list of antigens was provided to indicate which ones are included in the antigen match.

Transfusion

Due to the sometimes rapid progression of ACS, feasibility of prompt provision of the potentially preventive RBC transfusion was a primary objective of the study; therefore a transfusion history and blood bank records of all enrollees were required. Antibody histories and red cell phenotype data, if available, were obtained from blood banks at each site. Results of antibody screening from blood collected on enrollment and, for randomized subjects only, before and after each transfusion and at a follow-up visit on day 28 were collected.

Statistical Analysis

Alloimmunization prevalence was analyzed by transfusion history, site practice regarding antigen matching, age and (in adults) gender. Statistical analyses were performed at the Data Coordinating Center (New England Research Institutes, Watertown, MA) with SAS® release 9.2 (SAS Institute, Cary, NC). Descriptive statistics were reported as the number and percent, the mean and standard deviation/standard error, or the median and range. Differences in categorical variables were tested by chi-square or Fisher's exact test and differences in continuous variables were tested by t-test.

RESULTS

Prior to PROACTIVE termination due to inadequate accrual of randomized subjects, 237 patients (169 SS, 42 SC, 15 S β^0 -thalassemia, 11 S β^+ -thalassemia), 118 males and 119 females, were enrolled in the PROACTIVE trial from July 2009 through June 2010 by 26 centers, 2 to 27 patients (mean 9.5) per center. Alloimmunization was cited as a reason for exclusion of 27 of 378 (7.1%) subjects identified as potentially eligible for enrollment. Mean age of enrolled patients was 19.3 years (range 2.0–68.0); there were 122 children and 115 adults (age \geq 18 years). More than three quarters of the participants had received at least a single transfusion of red blood cells prior to the study; more than two thirds of children under age 10 had been transfused (Table I). Forty-five percent of adults over age 35 had received 10 or more transfusions.

Blood bank data were reported on 236 subjects. Thirty-four patients (14.4%), 14 (11.5%) children and 20 (17.4%) adults ($p=0.19$), had a history of at least one alloantibody and 17 of these had more than one. There was no difference in alloimmunization between adult men (15.7%) and women (18.8%) ($p=0.28$). Alloimmunization prevalence by age and transfusion load is depicted in Table I. Among children, 9 of 56 (16.1%) with 1–5 transfusions had alloantibodies compared to 4/17 (23.5%) with >10 transfusions ($p=0.48$). Four of 32 (12.5%) adults with 1–5 transfusions were alloimmunized compared to 10/31 (32.3%) those with >10 transfusions ($p=0.07$). The alloimmunization rate of heavily transfused subjects

was no different between adults and children ($p=0.74$). Antibodies were reported against D (2), C (9), E (9), e (5), V (2), Kell (K) (4), Js^a (1), Kp^a (3), Kp^b (2), Fy^a (3), Fy^b (2), Jk^a (1), Jk^b (2), Le^a (2), M (4), S (3) and other (11, including 5 autoantibodies). Looking only at those 179 patients who had received at least one transfusion, 33 (18.4%), 14 (15.4%) children and 19 (21.6%) adults ($p=0.28$), had a history of at least one alloantibody and 16 of these had more than one; unfortunately, one subject with no reported transfusions had a blood bank history of alloantibodies to anti-D, anti-C, anti-E, anti-e, anti-Fy^b and anti-Jk^a (likely indicating incomplete data reporting for this individual). Only 18 participants (12 adults, 6 children) had antibodies detectable on screening of blood specimens obtained at enrollment; 10.5% of adults and 5.0% of children had detectable antibodies ($p=0.11$).

When surveyed prior to commencement of PROACTIVE, 9 of 11 responding centers said that they performed red cell phenotyping for their patients with SCD; one center did not, and one performed red cell phenotyping only for adult patients. After the termination of the study twenty-three sites (88%) responded to the follow-up survey regarding pre-transfusion antigen typing. Nineteen centers (83% of responders) reported antigen matching beyond ABO/Rh and known antibodies for all transfusions (one for genotype Hb SS only); three did this only if one (two sites) or more (one site, for chronic transfusion patients only) antibodies were known to be present, and one center “on a case-by-case basis”. There was no difference in antibody prevalence between the four centers that did not routinely provide antigen matched blood (13.7%) and those that did (14.8%) ($p=0.85$); within the latter group, there was no difference between those that limited matching to C, E and K antigens (14.8%) and those that did more extensive matching (14.7%) ($p=0.99$). Eleven sites matched for Duffy antigens (Fy^a and Fy^b).

DISCUSSION

Individuals with SCD frequently require transfusion of red blood cells to treat acute complications, and chronic transfusion is recommended for primary¹² and secondary¹³ stroke prevention; it appears use of transfusion has increased over the last several decades. In a report from the CSSCD, a large natural history study of sickle cell anemia in the 1980's, only approximately 50% of enrolled subjects had a history of transfusion at entry,¹¹ as compared to 75.8% having a history of transfusion in PROACTIVE. It may be that transfusion is more frequently utilized today than during the CSSCD due to improved safety of the blood supply,¹⁴ documentation by the Stroke Prevention (STOP) trials of the need for indefinitely prolonged chronic transfusion for primary stroke prevention^{15,16} and the perception that transfusion improves outcomes of patients with acute chest syndrome.^{17–19} Acute chest syndrome is a leading cause of sickle cell-related hospitalization and, whereas during the CSSCD (1979–87) 26% of subjects with ACS were therapeutically transfused,²⁰ during the National ACS Study (1993–7), a similar large multi-institutional observational study, 72% of ACS patients received blood.²¹

CSSCD data were chosen for comparison since both the CSSCD and PROACTIVE were multi-institutional trials that involved centers with large sickle cell populations and expertise in their care. However, whereas all patients under care at participating institutions were eligible for entry into the CSSCD, PROACTIVE enrollees consisted only of individuals

hospitalized for pain. SCD patients with pain are more likely to have higher hemoglobin levels^{22,23} and thus perhaps a lower risk for transfusion. Higher hemoglobin levels are also seen in patients susceptible to ACS,^{22,24} a major indication for red cell transfusion, perhaps biasing PROACTIVE in the other direction, since ACS is a common indication for transfusion and thus risk for alloimmunization. The higher frequency of a history of transfusion overall in the PROACTIVE group as compared to the CSSCD would potentially increase the risk of alloantibodies.

The rate of alloimmunization of patients with SCD is higher than that of the general population, reaching 47% in one series,²⁵ perhaps largely related to antigen disparity due to differences in ethnic heritage between donors and recipients;³ in addition, blood cell antigens Rh (particularly D) and are the most alloimmunogenic.^{3,4,26–28} Not only does allosensitization put patients at risk for acute and delayed hemolytic transfusion reactions, sometimes severe,¹ but also can make a search for compatible blood difficult and costly for blood banks and providers. Antigen-matching may reduce alloimmunization.^{6–9,29} As demonstrated by our survey, the vast majority of our PROACTIVE sites insist on compatibility of these antigens even for non-sensitized patients, yet antibodies to C, E and remain the most commonly identified in our population.

Has this policy helped? Despite nearly universal attempts by PROACTIVE-participating sites to reduce the alloimmunization rate in their patients by extending antigen compatibility to at least the most problematic antigens (C, E and) and often further, the alloimmunization rate remains high (14.4%; 18.4% among those by history receiving at least one transfusion) among enrolled subjects; additionally, 7.1% of potentially eligible subjects could not be enrolled to PROACTIVE due to concern that existing alloantibodies might preclude prompt transfusion, if so randomized. Site practice regarding antigen matching did not impact on alloantibody prevalence in their PROACTIVE subjects, and there was no substantive reduction even among children, who should have most benefitted from recent recommendations for antigen matching. Unfortunately, we have no specific data from PROACTIVE sites as to when antigen matching was adopted. It is somewhat surprising that transfusion load did not appear to affect alloimmunization rates in either age group, though there was a trend toward a higher prevalence of alloantibodies in adults with more transfusion exposures as opposed to fewer.

The CSSCD documented by blood bank history and serologic screening prior to transfusion (90% concordant) that the overall alloimmunization rate upon enrollment to the study, 12.5%, was similar to that of PROACTIVE patients;¹¹ the SS genotype and increasing age were associated with a higher risk of alloimmunization. It is possible that antibody histories available during the CSSCD may have been less comprehensive than available today or that the current computerized records are more accurate and yield more complete results; the true alloimmunization rate may have been higher. In addition, current methods of antibody detection are more sensitive than those used at the time of the report in 1990, raising the possibility that these data reflect better detection, not a similar alloimmunization rate.

In a survey of those selected to participate in the National Heart Lung and Blood Institute-supported Comprehensive Sickle Cell Centers, 71% of responding centers indicated antigen-

this practice be considered standard of care for all patients with SCD who require transfusion.

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Table 1

Transfusion History at Enrollment by Age Group

Number of prior red cell transfusions	Age group				Total (N=236)	
	2-9 years (N=44)	10-17 years (N=78)	18-35 years (N=92)	36+ years (N=22)	Number of patients with alloantibody (N=34)	Total Number of patients (%)
None	Number of patients with alloantibody (N=3): 0	Number of patients with alloantibody (N=11): 0	Number of patients with alloantibody (N=15): 1	Number of patients with alloantibody (N=5): 0	1	57 (24.2)
1-5	Total Number of patients (%): 20 (45.5)	Total Number of patients (%): 36 (46.2)	Total Number of patients (%): 27 (29.3)	Total Number of patients (%): 5 (22.7)	13	88 (37.3)
5-10	Number of patients with alloantibody (N=3): 0	Number of patients with alloantibody (N=11): 1	Number of patients with alloantibody (N=15): 4	Number of patients with alloantibody (N=5): 1	6	43 (18.2)
>10	Total Number of patients (%): 5 (11.4)	Total Number of patients (%): 12 (15.4)	Total Number of patients (%): 21 (22.8)	Total Number of patients (%): 10 (45.5)	14	48 (20.3)