Red cell alloimmunization in transfused patients: A silent epidemic revisited

Hemchandra Pandey, Sudipta Sekhar Das[1], Rajendra Chaudhary

Departments of Transfusion Medicine, SGPGIMS, Lucknow, Uttar Pradesh, [1]Apollo Hospitals, Kolkata, West Bengal, India

Access this article online
Website: www.ajts.org
DOI: 10.4103/0973-6247.137433
Quick Response Code:

Correspondence to:
Prof. Rajendra Chaudhary, Department of Transfusion Medicine, SGPGIMS, Lucknow, Uttar Pradesh, India.
E-mail: rkcsgpgi@gmail.com

Alloimmunization consists of the induction of immunity in response to foreign antigen(s) encountered through exposure to cells or tissues from a genetically different member of the same species.[1] It is one of the major complications of regular blood transfusions, particularly in patients who are chronically transfused. Blood group antigens can be immunogenic in individuals who lack the corresponding antigen on their red blood cells (RBCs). This mismatch can occur during transfusion of antigenpositive blood into someone who is antigen-negative, or during pregnancy when the mother lacks a blood group antigen that is contained on the fetal RBCs. In the former case, this can result in immunization of the transfusion recipient and the production of alloantibody that may cause a hemolytic transfusion reaction.[2]

Observational studies in random patients, who most often receive incidental transfusions, and pregnant women estimated the antibody prevalence between <1-3%. This incidence increases in multiply transfused patients and transfusion-dependent patients which include patients with sickle cell disease (SCD), severe thalassemia syndromes, severe aplastic anemia, myelodysplastic syndromes, and other congenital or acquired chronic anemias. The incidence in these patient groups has been reported to vary from 8% to 76% among different countries.[3]

The reported prevalence of alloimmunization in multi-transfused patients in India is comparatively low varying from approximately 3% to 10%.[4-6] In the study by Dhawan *et al.*[7] in this journal, the incidence of red cell alloimmunization is relatively low (5.64%), which is in accordance with studies from India. This low rate of alloimmunization may be explained by the presumed high phenotypic compatibility between blood donors and the patients. The genetic disparity between patient and donor RBC phenotypes is considered to be the main reason for the high immunization risk in patients with SCD in USA. Especially, C, Fya, Fyb, Jkb and S RBC antigens are significantly less frequent ($P < 0.001$) in the predominantly black sickle cell patients than in the predominantly white donors[8] and antibodies against these antigens are more frequently found than in most other patients. Studies in sickle cell patients performed in Jamaica[9] with a closer racial matching of donor and recipients, showed a 3 times lower immunization risk compared with European and American studies (9% vs. 27%). This led to the policy to prophylactically match donor RBCs for RH and K antigens in patients with hemoglobinopathies.

Other factors implicated in RBC alloantibody formation include recipient sex and age, history of pregnancy, number and timing of blood transfusions, recipient clinical diagnosis and treatment, genetic factors related to the antigenic response, and racial differences between donors and recipients.[10] The formation of red cell antibodies may be influenced by the patients' age at which the transfusions are given or when chronic transfusion therapy is started. Four studies on RBC alloimmunization performed in (preterm) neonates who received multiple transfusions during the first 3-4 months of life did not encounter any RBC antibodies.[11] Furthermore, in hemoglobinopathy patients it has been shown that alloimmunization risk was significantly lower in patients who started transfusion therapy at a very young age (<3 years) compared with those who started later in life.[12] Dhawan *et al.*[7] in this issue also observed the same. Age at first transfusion was significantly higher in alloimmunized (23.28 months) than nonimmunized patients (14.43 months) ($P = 0.042$). An immature immune system and some form of acquired immune tolerance to allogeneic RBC antigens are held responsible for the reduced alloimmunization risk.

Other than ABO antibodies most other clinically significant antibodies to red cell surface antigens are immunoglobulin G (IgG) and produced in response to immunization by antigen-positive red cells: Either donor red cells following transfusion or cells of fetal origin, following fetomaternal hemorrhage during pregnancy or at parturition.[3] The antigens most frequently involved in alloimmunization belong to the Rh, Kell, Kidd, Duffy, Lewis and MNS blood group systems.[10] Dhawan *et al.*[7] in this issue also reported that out of total 23 alloantibodies detected

in 319 transfused thalassemic patients, 87.17% belonged to Rh and Kell blood group system.

These antibodies may result in clinically significant hemolytic transfusion reactions, difficulty in cross-matching blood, decrease in RBC survival and an increased transfusion requirement.[13] In addition, downstream effects resulting from RBC clearance can lead to multiple organ failure, electrolyte perturbations, coagulopathy, and in some cases, death. Humoral alloimmunization to RBC antigens is thus a significant clinical problem.

It is thus important to detect these alloantibodies in a timely fashion so that antigen-negative blood could be provided to patients. Antibody screening is commonly done by indirect coombs test by utilizing screening cell panels as most clinically significant antibodies are of IgG type. Traditionally, these cell panels are procured from the western countries and thus they represent the antigens commonly present in western populations in addition to being costly and difficult to procure. It is thus important to develop cell panels derived from local ethnic groups so that clinically significant antibodies against antigens in local population could be detected such as antibodies to In (b–) in Asians.[3,6] However, this approach of providing antigen-negative blood after development of alloantibody is time consuming and costly and at times it becomes difficult to provide antigen-negative blood to patients who have developed multiple alloantibodies. It is thus important to adopt policies for prevention of alloantibody formation in multi-transfused or transfusion-dependent patients.

In addition to alloantibodies, chronically transfused thalassemics are also prone to develop red cell autoantibodies, which can complicate transfusion therapy further. Dhawan *et al*.[7] in this issue of journal reported 28.2% of their patients developed autoantibodies. The pathogenesis of erythrocyte autoantibody formation following transfusion is not well-understood. However, clinical evidence of autoimmune haemolytic anaemia (AIHA) has been seen with high amounts of RBC-associated IgG.[14] It was also suggested that alloantibody binding to the RBCs could lead to conformational changes of the antigenic epitope that ultimately stimulates production of autoantibodies.[15] It is possible that certain people are genetic responders who have an increased tendency to develop RBC autoantibodies and the tendency toward autoantibody formation could reflect an overall dysfunction of the immune system.[16]

Red cell autoantibodies can result in clinical hemolysis called AIHA, and in difficulty in cross-matching blood. Patients with autoantibodies may have a higher transfusion rate and often require immunosuppressive drugs or alternative treatments including intravenous IgG and rituximab (anti-CD20 monoclonal antibody). Philip and Jain 2014[17] in this issue reported a case of thalassemia patient who developed autoantibodies with severe hemolysis and difficulty in finding suitable unit of blood. The case was successfully managed by Rituximab along with extended phenotype matched blood. However, one should be careful in interpretation of positive direct antiglobulin test (DAT) in a multi-transfused patient as delayed hemolytic reactions can also give rise to positive DAT, mixed field reaction and clinical hemolysis. This should be ruled out by elution and serial monitoring of DAT in such patients.

Approaches for prevention or treatment of alloimmunization range from provision of RBCs matched for all the major antigens associated with clinically significant antibodies to blood matched only for antibodies that have already been made. In the first approach an extended RBC phenotype (ABO, Rh, Kell, Kidd, Duffy, Lewis, MNS) of the patient is done before commencing transfusion therapy and antigen-matching for C, E and K antigens is performed for patients without prior alloantibody formation.[10] However, the expense and the feasibility of antigen-matched blood may not permit such a transfusion approach in some medical centers. For economic reasons, such centers can match the blood for antibodies common in their populations. The second approach involves transfusing matched blood only for patients who first proved to be "antibody producers" as this may reduce expenses and increase the availability of matched blood.[8]

References

1. Zimring JC, Welniak L, Semple JW, Ness PM, Slichter SJ, Spitalnik SL, *et al.* Current problems and future directions of transfusion-induced alloimmunization: Summary of an NHLBI working group. Transfusion 2011;51:435-41.
2. Daniels G, Poole J, de Silva M, Callaghan T, MacLennan S, Smith N. The clinical significance of blood group antibodies. Transfus Med 2002;12:287-95.
3. Poole J, Daniels G. Blood group antibodies and their significance in transfusion medicine. Transfus Med Rev 2007;21:58-71.
4. Lamba DS, Kaur R, Basu S. Clinically Significant Minor Blood Group Antigens amongst North Indian Donor Population. Adv Hematol 2013;2013:215454.
5. Shukla JS, Chaudhary RK. Red cell alloimmunization in multi-transfused chronic renal failure patients undergoing hemodialysis. Indian J Pathol Microbiol 1999;42:299-302.
6. Sood R, Makroo RN, Riana V, Rosamma NL. Detection of alloimmunization to ensure safer transfusion practice. Asian J Transfus Sci 2013;7:135-9.
7. Dhawan HK, Kumawat V, Marwaha N, Sharma RR, Sachde S, Bansal D, *et al*. Alloimmunization and autoimmunization in transfusion dependent thalassemia major patients. Study on 319 patients. Asian J Transfus Sci 2014;8:84-8.
8. Singer ST, Wu V, Mignacca R, Kuypers FA, Morel P, Vichinsky EP. Alloimmunization and erythrocyte autoimmunization in transfusion-dependent thalassemia patients of predominantly asian descent. Blood 2000;96:3369-73.
9. Olujohungbe A, Hambleton I, Stephens L, Serjeant B, Serjeant G. Red cell antibodies in patients with homozygous sickle cell disease: A comparison of patients in Jamaica and the United Kingdom. Br J Haematol 2001;113:661-5.
10. Natukunda B. Red blood cell alloimmunization and antigen matching in sickle cell disease — The African perspective. ISBT Sci Ser 2012;7:129-33.
11. Strauss RG, Johnson K, Cress G, Cordle DG. Alloimmunization in preterm infants after repeated transfusions of WBC-reduced RBCs from the same donor. Transfusion 2000;40:1463-8.
12. Spanos T, Karageorga M, Ladis V, Peristeri J, Hatziliami A, Kattamis C. Red cell alloantibodies in patients with thalassemia. Vox Sang 1990;58:50-5.
13. Pahuja S, Pujani M, Gupta SK, Chandra J, Jain M. Alloimmunization and red cell autoimmunization in multitransfused thalassemics of Indian origin. Hematology 2010;15:174-7.

14. Noor Haslina MN, Ariffin N, Illuni Hayati I, Rosline H. Red cell autoantibodies among thalassaemia patients in Hospital Universiti Sains Malaysia. Singapore Med J 2007;48:922-5.
15. Advani R, Sorenson S, Shinar E, Lande W, Rachmilewitz E, Schrier SL. Characterization and comparison of the red blood cell membrane damage in severe human alpha- and beta-thalassemia. Blood 1992;79:1058-63.
16. Castellino SM, Combs MR, Zimmerman SA, Issitt PD, Ware RE. Erythrocyte autoantibodies in paediatric patients with sickle cell disease receiving transfusion therapy: Frequency, characteristics and significance. Br J Haematol 1999;104:189-94.
17. Philip J, Jain N. Resolution of alloimmunization and refractory autoimmune hemolytic anemia in a multi-transfused beta thalassemia major patient. Asian J Transfus Sci 2014;8:128-30.

Cite this article as: Pandey H, Das SS, Chaudhary R. Red cell alloimmunization in transfused patients: A silent epidemic revisited. Asian J Transfus Sci 2014;8:75-7.

Source of Support: Nil, **Conflicting Interest:** None declared.