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Alloimmunization to red cells in thalassemics: Emerging problem and future strategies

Richa Gupta [a,*], Deepak Kumar Singh [b], Bharat Singh [c], Usha Rusia [b]

[a] Department of Lab Medicine, Chacha Nehru Bal Chikitsalaya, Geeta Colony, Delhi, India
[b] Department of Pathology, Guru Teg Bahadur Hospital, Delhi, India
[c] Regional Blood Transfusion Centre, Guru Teg Bahadur Hospital, Delhi, India

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ABSTRACT

Aims and objectives: To evaluate the magnitude of red cell alloimmunization in regularly transfused patients with thalassemia major and analyse factors responsible for development of antibodies.

Materials and methods: This cross sectional study was conducted on 116 thalassemics receiving regular transfusions. All the patients underwent antibody screening. Patients with positive antibody screen were further tested for antibody identification. The data was analysed to find out the frequency, pattern and factors influencing red cell alloimmunization secondary to multiple transfusions.

Results: Mean age of the patients was 14 years (range 1.5–27 years). Red cell alloantibodies were found in 11 patients (9.48%). In four (36%) patients first transfusion was given before 6 months of age and in seven (64%) patients, first transfusion was given after two years of age. The interval between consecutive transfusions varied from 18 to 35 days. The most common antibody was Anti-E found in 4 (36.4%) patients, followed by Anti-K (three patients, 27.2%), Anti-Kp^a (two patients, 18.2%) and Anti-C_w (two patients, 18.2%). The interval from first transfusion to antibody development varied from 1.5 to 14 years. None of the eight out of 116 patients, who underwent splenectomy showed any antibody development.

Conclusions: The rate of red cell alloimmunization was found to be 9.48% in thalassemics receiving regular transfusions. The incidence of alloantibody development was higher if first transfusion was received at more than 2 years of age. Early institution of red cell transfusions and Rh and Kell phenotyping followed by provision of matched blood could prevent alloimmunization.

1. Introduction

Life long red cell transfusion is the main supportive treatment for patients with thalassemia major. The use of regular transfusions & chelation therapy has transformed thalassemia from a fatal disease in early childhood to a chronic illness associated with prolonged survival [1]. However, the beneficial effect of each unit transfused is accompanied with the possibility of some adverse effects due to transfusion. The adverse affects more commonly seen in these patients due to repeated transfusions include – iron overload, increased rate of transfusion transmitted infections and alloimmunization to red cell antigens. The use of Desferroxamine and recently, orally administered iron chelator "Deferasirox" has considerably reduced hepatic iron accumulation in these patients with minimal side effects [2]. With the advent of newer screening tests like 4th generation ELISA and Nucleic Acid Amplification Technique (NAT), the risk of transfusion transmitted infections has also been considerably reduced.

* Corresponding author. Address: 132, Rajdhani Nikunj Apartments, 94 I.P. Extension, Patpadganj, Delhi 110092, India. Tel.: +91 9910790101, +91 9540951526.
E-mail address: richagupta0209@gmail.com (R. Gupta).

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Red cell alloimmunization remains a major challenge to repeat transfusions in these patients. Alloimmunization occurs when an incompatible antigen is introduced in an immunocompetent host. Formation of alloantibodies to red cell antigens may be stimulated by either transfusion of red cells or fetomaternal bleed. Though such antibodies are infrequently observed in patients receiving occasional transfusions, their development is much more common in patients receiving repeat red cell concentrates. The development of such antibodies can significantly complicate transfusion therapy due to the occurrence of acute and delayed type of haemolytic transfusion reactions, difficulty in finding compatible blood units and increased risk of haemolytic disease of the newborn when such a patient becomes pregnant [3]. Also, it can cause difficulty in haematopoetic bonemarrow/stem cell transplantation and increase the chances of graft rejection in patients who are candidates for such therapy in future.

Though antibody formation can take place against any antigen present on the surface of red cells, such antibodies have been more frequently observed against antigens belonging to the Rh and Kell blood group system [4].

The aims of the present study were (1) to determine the frequency of red cell alloantibodies in patients of thalassemia major receiving regular blood transfusions; (2) to analyse factors which may be responsible for the development of these antibodies; (3) to find out the type of antibody and extent to which provision of Rh and Kell matched blood could prevent alloimmunization in these patients.

2. Materials and methods

This study included 110 patients of thalassemia major receiving regular blood transfusions in the hospital. Clinical and transfusion records of all the patients were analysed to record parameters like age of the patient at the time of diagnosis, age at which first transfusion was given, intervals between transfusions and whether splenectomy was performed as a part of management. Patient parameters including haemoglobin, haematocrit, reticulocyte count, total and indirect bilirubin, results of haemoglobin electrophoresis, HbA, Hb A_2 and Hb F levels were also recorded.

Every time a patient came to receive transfusion, a 5 ml blood sample was collected in anticoagulant EDTA for antibody screening and identification. A sample without anticoagulant was also collected for blood grouping and cross matching. Sample for antibody screening was collected in an EDTA tube since plasma is preferable to serum when carrying out antibody screening by gel card method [5]. Plasma was separated by centrifugation at 1000 rpm for 2 min (Microcentrifuge, model-ID Centrifuge 24-S, By ID-Diamed, Switzerland). The separated plasma was divided into two aliquots and both were labelled with identification code of the patient.

Antibody screening was performed on one plasma sample and the other was kept at −30 °C in deep freezer for antibody identification in future in case of a positive antibody screen. Screening for alloantibody was done by gel card technology using three cell panel (ID-Diacell I-II-III, Diamed, Switzerland). The antibody screen of each sample was done by a trained transfusion technologist without knowledge of the corresponding patient details. The screening cell panel covered antigens of all known blood groups including Rh, Kell, Kidd, Duffy, P, Lewis, MNS, Lutheran and Xg. The reaction was performed in both Coombs and Enzyme phase to increase the sensitivity of the procedure. For enzyme phase of reaction papainized cells (ID-Diacell I-II-III-P, Diamed, Switzerland) available readymade with the manufacturer were used. Grading and scoring of the agglutination in the gel cards was done by doctors without knowledge of the clinical and laboratory data of the patient. The grading and scoring was done according to the distribution of agglutination throughout the gel matrix as shown in Fig. 1.

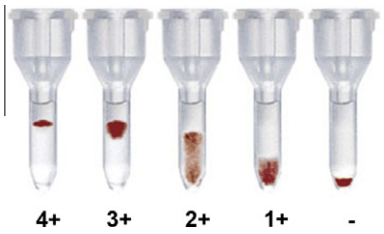

Fig. 1. Grading of reaction using gel technology.

In case of a positive result on initial screen, antibody identification was done using the 11 cell identification panel (ID DiaPanel, Diamed, Switzerland). An autocontrol was also put simultaneously to exclude the presence of autoantibody.

3. Results

A total of 116 patients of thalassemia major were included in this study. The age of the patients ranged from 1.5 to 27 years with a mean age of 14.25 years. There were sixty males and fifty-six females (M:F ratio of 1.07:1). All of them received regular transfusion with leukodepleted red cell concentrates during a period ranging from 1 to 26.6 years.

Out of total 116 patients, 11 (9.48%) patients developed alloantibodies. Profile of patients with alloantibodies is shown in Table 1. Out of 11 patients with alloantibodies there were seven males and four females. In seven patients (63.6%) transfusion was initiated after two years of age. The time interval between transfusions in these patients varied from 18 to 35 days. None of these 11 patients who developed alloantibodies underwent a splenectomy. Six patients out of 116 had undergone splenectomy due to increase in the requirement of blood but none of the splenectomised patient developed alloantibodies.

The antibody characteristics of all the 11 patients were also studied (Table 2). The most common antibody was found to be Anti E (present in 4 cases) followed by Anti K which developed in 3 cases. Anti C_w and Anti Kp^a developed in two patients each. There was one patient who developed multiple antibodies (Anti E and Anti Kp^a). Majority (7/12) of the antibodies belonged to the Rh blood group system and the rest (5/12) belonged to the Kell