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Screening and identification of red blood cell alloantibodies among hemodialysis patients in National Institute of Urology and Nephrology

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Screening and identification of red blood cell alloantibodies among hemodialysis patients in National Institute of Urology and Nephrology

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Abstract

Background

It is well known that alloimmunization to red blood cell antigens resulting from the genetic disparities between the donor and the recipient is one of the risks of blood transfusion. Alloimmunization can result in clinical hemolysis and difficulty in cross-matching blood. The risk of alloimmunization is higher in patients who have received multiple blood transfusions such as renal failure patients on dialysis who receive blood transfusions. The antibody-screening test (2–3 cells panel) used to detect unexpected antibodies is not a mandatory pretransfusion testing in our blood bank of National Institute of Urology and Nephrology (NIUN), and is performed routinely in limited blood centers.

Aim

This study was conducted to screen and identify different types of red cell alloantibodies and the factors influencing the development of alloantibodies among patients on dialysis in NIUN.

Patients and methods

This study was conducted in the blood bank of NIUN, Egypt. A total of 192 patients (102 males and 90 women) who were diagnosed to have chronic renal failure, on regular hemodialysis for at least 1 year, their age more than 20 years, anemic (hemoglobin <8 g/dl), and with a previous history of blood transfusion for at least once were selected for the study. All patients' sera were subjected to the following tests: antibody screening, patients' sera were tested against three panels of commercially prepared group O cells and antibody identification, positive patients' sera by a screening test, and retested against commercial panels of 11 cells.

Results

Red cell alloantibodies were detected in 10 (5.2%) patients (two men and eight women). The prevalence of alloantibodies detected in patients with positive results were anti-E (2.1%), anti-K (1.6%), antibodies of unknown specificity (1.6%), and antibody against high-incidence antigen (0.5%). There was a significant difference between sex and the number of blood units transfused with alloimmunization ($P = 0.048$ and 0.037, respectively).

Conclusion

The prevalence of alloimmunization among chronic renal failure patients on dialysis was 5.2%. The most common alloantibodies were anti-E (the Rhesus system) (2.1%) and anti-K (the Kell system) (1.6%) and the risk of alloimmunization is known to be influenced by the recipient sex (more in females) as well as the number of blood units transfused. So, antibody screening and identification tests are recommended as a routine pretransfusion testing protocol at least for the patients who are at higher risk of alloimmunization and require long-term transfusion dependence, which will definitely add significant value in blood safety.

Keywords: Alloimmunization, anemia, chronic renal failure

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INTRODUCTION

Red blood cell (RBC) transfusions are a very important healthcare practice especially for patients of thalassemia, myeloproliferative disorders, leukemia, and end-stage renal failure. Chronic RBC transfusions can cause unwanted complications to the patient called transfusion reactions. Development of alloantibodies to RBC antigens is an important immune-mediated delayed hemolytic transfusion reaction. It is a matter of great concern in multitransfused patients and in patients who have had multiple pregnancies [1]. RBC alloantibodies other than non-RBC stimulated anti-A or B are called unexpected RBC alloantibodies and may be found in 0.3–38% of the population upon the group of the patients or donors studied and the sensitivity of the test methods used in blood banks. The RBC antigens and their alloantibodies vary among different human populations and ethnic groups [2].

Alloimmunization results from the disparity between the donor and patient antigens; prior exposure to donor antigens can lead to an anamnestic or secondary response where even very small amounts of donor antigenic RBCs can elicit an alloimmune response resulting in an increase in antibody production leading to RBC destruction as the patient is already immunized [3]. The degree of clinical significance may vary even among antibodies with the same specificity; some antibodies cause the destruction of incompatible cells within hours or even minutes; others decrease the survival by only a few days; and some cause no discernible cell destruction. Development of alloantibodies thus complicates and limits transfusion therapy, contributing not only to technical complications but also to morbidity and mortality [4].

Serological safety is an integral part of overall safety for the blood bank. Alloantibodies to RBC antigens may be initially detected in tests that use patients' serum including ABO testing, cross-match testing, and the antibody detection test [5]. This study was conducted to screen and identify different types of RBC alloantibodies among patients on dialysis in National Institute of Urology and Nephrology and the factors influencing the development of alloantibodies in the hope to overcome difficulties in cross-matching of their blood with the blood units and giving antigen-negative blood to alloantibody-positive patients and minimizing complications of blood transfusion in those patients.

PATIENTS AND METHODS

This study was performed in the blood bank of National Institute of Urology and Nephrology, Egypt. A total of 192 (102 men, 90 women) patients who were diagnosed to have chronic renal failure (CRF), on regular hemodialysis for at least 1 year, their age more 20 years, anemic (hemoglobin <8 g/dl), and with previous history of blood transfusion for at least once were included in the study. Patients with previous transplantation, systemic autoimmune diseases or on cortisone therapy were excluded from the study. All patients signed an informed written consent with their acceptance for participating

in this study after explaining the value of our study. Clinical data were recorded, with reference to age, sex, and the total number of blood units given.

All patients' sera were subjected to the following tests: antibody screening, patients sera were tested against three panels of commercially prepared group O cells obtained from donors that are phenotypic for the most commonly encountered and clinically important RBC antigens (Biokit, Barcelona, Spain). Antibody identification; positive patients' sera by screening test, retested against commercial panels of 11 cells in the same phases as antibody-screening test (Biokit), using cross-matched cards (Grifols Movaco, Barcelona, Spain).

Statistical methods

Data were analyzed using Stata, version 14.2 (StataCorp LLC, College Station, Texas, USA). Normality of numerical data distribution was examined using the Shapiro–Wilk test. Non-normally distributed numerical data were presented as median and interquartile range and intergroup differences were compared using the Wilcoxon rank-sum test. Categorical data were presented as number and percentage and differences were compared using Fisher's exact test. A P value less than 0.05 was considered statistically significant.

RESULTS

A total of 192 patients diagnosed to have CRF, on regular hemodialysis for at least 1 year, aged from 20–69 years, anemic (hemoglobin <8 g/dl), and with previous history of blood transfusion for at least once. There were 102 (53.1%) men and 90 (46.9%) women (Table 1). Men received an average of 2 U and women received an average of 4 U. RBC alloantibodies were detected in 10 (5.2%) patients (two men and eight women) and 182 (94.8%) patients had no alloantibodies (Table 2). The prevalence of alloantibodies detected in patients with positive results were anti-E (2.1%), anti-K (1.6%), antibodies of unknown specificity (1.6%) and antibody against high-incidence antigen (0.5%) (Table 3 and Fig. 1). Statistical analysis of our results indicated a significant difference between sex and the number of blood units transfused with alloimmunization ($P = 0.048$ and 0.037, respectively) (Table 4 and Figs. 2-4).

DISCUSSION

Anemia is a severe complication of chronic kidney disease that is common in more than 80% of patients with impaired renal function. Although there are many mechanisms involved in the

Table 1: Demographic characteristics of the study population

Variables	Median (interquartile range), range/*n* (%)
Age (years)	49 (39-56), 20-69
Sex	
Male	102 (53.1)
Female	90 (46.9)
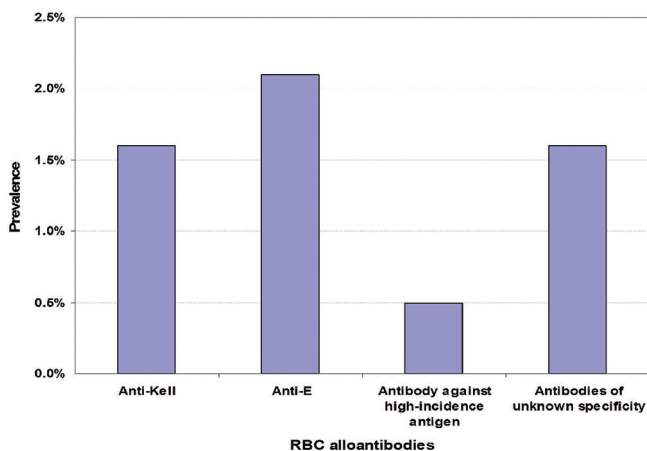
Figure 1: Prevalence of individual alloantibodies in the study. RBC, red blood cell.

Figure 2: Box plot showing the age of patients with positive or negative red blood cell (RBC) alloantibodies. Box represents the range from the first quartile to the third quartile (interquartile range). The line inside the box represents the median (second quartile). Error bars represent the minimum and maximum values.

Table 2: Prevalence of red blood cell alloantibodies among the study

Variables	*n* (%)
Negative	182 (94.8)
Positive	10 (5.2)

Table 3: Prevalence of individual red blood cell alloantibodies among the study

Variables	*n* (%)
Anti-Kell	3 (1.6)
Anti-E	4 (2.1)
Antibody against high-incidence antigen	1 (0.5)
Antibodies of unknown specificity	3 (1.6)
No red blood cell alloantibody	182 (94.8)

Table 4: Comparison of patients with positive or negative red blood cell alloantibodies as regards age, sex, and number of transfused blood units

Variables	Negative (*n*=182)	Positive (*n*=10)	P*
Age (years)	50 (37-56)	45 (40-56)	0.783
Sex			**0.048**
Male	100 (54.9)	2 (20.0)	
Female	82 (45.1)	8 (80.0)	
Number of transfused blood units	2 (1-3)	4 (2-6)	**0.037**

*$P < 0.05$ Statistically significant Data are represented as median (interquartile range) or *n* (%).

pathogenesis of anemia (iron, folate, or vitamin B_{12} deficiency; gastrointestinal bleeding; severe hyperparathyroidism; systemic inflammation; and shortened RBC survival), the primary cause is the inadequate production of erythropoietin by the damaged kidneys [6].

Alloantibodies arise in CRF patients after exposure to repeated RBC transfusion due to anemia and RBC alloimmunization results from th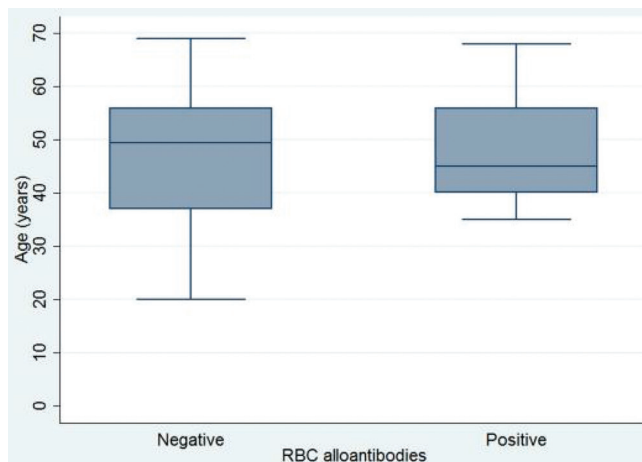e disparity of antigens between the donor and the recipient. Recipient's immune status, immunogenicity of the antigen, and dose of the antigen are the factors, which play a significant role in alloimmunization that results in difficulty in obtaining compatible blood, transfusion reactions, hemolysis, and occasionally life-threatening events [7]. RBC alloantibody formation is a common complication among CRF patients who need regular transfusion therapy in which the corresponding antigen-negative matched blood is required for safer transfusion [8].

Our study was done to determine the frequency and specificity of RBC alloantibodies among the CRF patients on dialysis so making over difficulties in cross-matching of their blood with the blood units and giving antigen-negative blood to alloantibody-positive patients.

In our study, we found that the prevalence of alloimmunization among CRF patients on dialysis were 5.2%, which was less than Shukla and Chaudhary [9] who discovered an alloimmunization rate of 9.8% in CRF patients undergoing hemodialysis. Also, the study was done by Patel *et al.* [10] who had shown that am alloimmunization rate of 8.2% in CRF patients and Babiker and Elsayed [7] who reported that the alloimmunization rate was 13.1% in 11 out of 84 CRF. Our results were nearly like that of Domen and Ramirez [11], who reported a low rate of 6.1% of antibody formation in CRF and also in agreement with that of Natukunda *et al.* [12], who reported an alloimmunization rate of 6.1% in multiple transfused patients and Jain *et al.* [13] who demonstrated that the rate of RBC alloimmunization was 5.21% in multiply transfused thalassemia major patients.

In contrast to our study, Amit *et al.* [14] study, in which 258 multitransfused patients were studied, seven (2.71%) patients were found alloimmunized. The risk of alloimmunization was 0% in CRF patients, 2.90% in thalassemia patients, 3.77% in pregnant women with bad obstetric history, and 2.78% in other multitransfused patients like those with cancer [14].
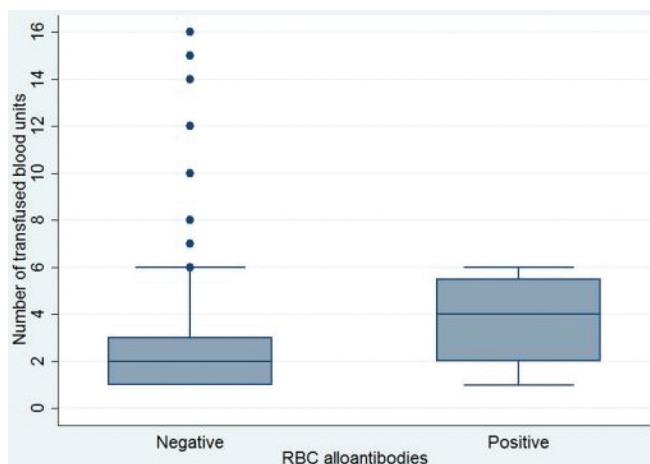
Figure 3: Box plot showing the number of transfused blood units in patients with positive or negative red blood cell (RBC) alloantibodies. The box represents the range from the first quartile to the third quartile (interquartile range). The line inside the box represents the median (the second quartile). Error bars represent the minimum and maximum values excluding the outliers (rounded markers).

The disparity in the alloimmunization rate was attributed to several diverse patient population, racial factors, and RBC antigenic difference between the donor and the recipient, recipient immune system, pretransfusion blood tests that were matched only for ABO and Rh (D) antigens, sample size of the study population, and sensitivity of the test method [15].

The low alloimmunization rate in our study suggests that there is the homogeneity of RBC antigens in recipients and blood donors in the Egyptian community.

In our study, we found that the most common alloantibodies among hemodialysis patients were anti-E (the Rhesus system) (2.1%) and anti-K (the Kell system) (1.6%), and this finding was matched with the results obtained by Shukla and Chaudhary [9], who observed that nine alloantibodies were detected in eight patients, and the most involved antigens were the Rhesus and the Kell systems (88%); also Makroo *et al.* [5] found that positive cases for irregular alloantibodies from 109 cases of CRF were four (3.7%) and the most frequent was anti-E, anti-C, and anti-K. Similarly, in a study conducted by Babiker and Elsayed [7] and Patel *et al.* [10] who reported that the most common alloantibodies among CRF patients were C (the Rhesus system) and anti-K (the Kell system) [7,10]. These findings suggest that it is important to perform extended typing for chronically transfused patients at least for Rh and Kell antigens before the initial RBC transfusion. For this purpose, it is also rational to have already typed RBC in the blood supply.

In our study, we found a significant difference between a number of units transfused and alloimmunization ($P > 0.037$). Our results were in agreement with a number of studies: Babiker and Elsayed [7], Thakral *et al.* [16], and Hundric-Haspl *et al.* [17], who reported an increasing number of alloimmunized patients dependent on the number of RBC units transfused [7,16,17].
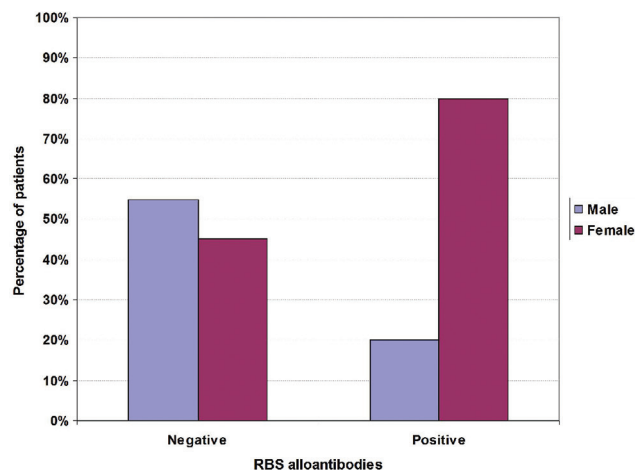

Figure 4: The percentage of either sex among patients with negative or positive red blood cell (RBC) alloantibodies.

However, Shukla and Chaudhary [9] failed to find a correlation between alloimmunization and the number of RBC units transfused.

In addition, we found that the prevalence of RBC alloimmunization in women was higher (9.7%) than men (2%) and the difference was significant ($P > 0.048$). The same observation was also mentioned by Babiker and Elsayed [7] and also in thalassemia patients by Jain *et al.* [13]. This is likely explained by more exposure to immunizing antigens through pregnancy and more transfusions in women as in our study. However, Verduin *et al.* [18] found that older female patients are an independent risk factor for RBC alloimmunization after transfusion.

Multitransfused patients are always at higher risk of alloimmunization and this creates difficulty in their pretransfusion testing. Therefore, antibody screening and identification tests are recommended as a routine pretransfusion testing protocol at least for the patients who are at higher risk of alloimmunization and require long-term transfusion dependence. Finally, this will definitely add significant value in blood safety. However, further research work is recommended to establish the steps and methods of this protocol.

Conclusion

The prevalence of alloimmunization among CRF patients on dialysis was 5.2%. The most common alloantibodies were anti-E (the Rhesus system) (2.1%) and anti-K (the Kell system) (1.6%) and the risk of alloimmunization is known to be influenced by the recipient sex (more in women) as well as the number of blood units transfused.

Conflicts of interest
There are no conflicts of interest.

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