

## Original Research Article

# Red cell alloimmunization and autoantibodies in transfusion dependent thalassemia patients of Jammu region

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## ABSTRACT

**Background:** Thalassemia is one of the most common genetic disorder of hemoglobin synthesis in Jammu region. Although RBC transfusion is life saving for these patients, it may be associated with some complications like RBC alloimmunization. Thus, alloimmunization against red blood cell antigens increases the need for transfusion and can significantly complicate transfusion therapy. Therefore, screening for unexpected antibodies should be a part of all pretransfusion testing, with antibody identification in the event of a positive result. The aim of the study was to determine the frequency of alloimmunization and autoimmunization and the most common alloantibodies involved.

**Methods:** This was a descriptive study involving a total of 146 thalassemic patients in the age range of 2-32 years receiving regular blood transfusions, registered at SMGS blood bank, Jammu. Antibodies screening, antibody identification, and cross matching was done on all patient samples included in the study, during the period between November 2014 and October 2015.

**Results:** At the start of the study, 8 patients who tested positive for alloantibodies 3 patients had more than one antibody subtype. Anti-E was the commonest antibody found in 4 (50%) patients. Similarly, at the end of study, antibody screening and then identification revealed presence of antibodies in 10 patients. Only 1 patient had more than one antibody subtype. Anti E was again the commonest antibody found in 5 (50%) patients.

**Conclusions:** The most common alloantibodies identified were anti Rh system antibodies (anti-E and anti-D) followed by Kell antibodies. In order to reduce alloimmunization, a policy for performing extended red cell phenotyping of these patients is essential and at least antigen E and Kell negative blood should be provided for transfusion to these patients.

**Keywords:** Alloantibodies, Thalassemia, Splenectomy

## INTRODUCTION

The thalassemias are a group of inherited hematologic disorders caused by defects in the synthesis of one or more of the hemoglobin chains. In India, it is estimated that nearly 8,000-10,000 new thalassemics (homozygous) are born every year and beta thalassemia gene is found more commonly in Punjabis, Sindhis, Bengalis, and Gujratis.<sup>1</sup> The primary pathology in thalassemia stems from the

reduced quantity of globin chain production. The globin chains that are produced in relative excess can damage the red cells or their precursors. As a result, there is an overall deficit of hemoglobin tetramers in the Red blood cells (RBC) and the Mean corpuscular volume (MCV) and Mean corpuscular hemoglobin (MCH) are reduced.<sup>2</sup>

The thalassemia syndrome is classified according to which of the globin chains,  $\alpha$  or  $\beta$ , is affected. These 2 major

groups,  $\alpha$  and  $\beta$ -thalassemia, are sub classified according to absent ( $\alpha 0$  and  $\beta 0$ ) or reduced ( $\alpha +$  or  $\beta +$ ) globin chain synthesis.<sup>3</sup> In  $\beta$  thalassemia major there is an inadequate production of  $\beta$  globin chains and thus an imbalance in  $\alpha$  and  $\beta$  globin chain production causing severe anemia (Nelson textbook of paediatrics).

Children with  $\beta$  thalassemia usually become symptomatic from progressive hemolytic anemia, with profound weakness and cardiac decompensation during the 2<sup>nd</sup> to 6<sup>th</sup> month of life as foetal hemoglobin HbF synthesis diminishes. Regular blood transfusions remain the mainstay of treatment for these children. The combination of transfusion and chelation therapy has dramatically extended the life expectancy of these patients. Although blood transfusion is a life saver for thalassemia patients, it may be associated with some complications such as iron overload, platelet and RBC alloimmunization.<sup>4,5</sup>

Repetition of transfusions for the treatment of thalassemia major provokes the patient's immune system and produces anti-erythrocyte antibodies (alloantibody and/or autoantibody). Erythrocyte auto antibodies appear less frequently, but they can result in clinical hemolysis and in difficulty in cross-matching blood. Alloimmunization against red blood cell antigens increases the need for transfusion and can significantly complicate transfusion therapy.

The rates of alloimmunization in patients of thalassemia major in different parts of the world ranges from 5-30%.<sup>6</sup> Therefore, screening for unexpected antibodies should be a part of all pretransfusion testing, with antibody identification in the event of a positive result.<sup>7</sup> Some studies regarding alloantibody formation with similar results have also been carried out in India.<sup>8</sup>

### **Aims and objectives**

The aim and of this study were to determine the frequency of alloimmunization and the most common alloantibodies involved, and to determine the frequency of autoantibodies.

### **METHODS**

This was a descriptive study involving a total of 146 thalassemic patients in the age range of 2-32 years attending thalassemia day care center who received regular moderate transfusion regime in the department of transfusion medicine and immunohaematology, Shri Maharaja Gulab Singh Hospital, Government Medical College, Jammu from November 2014 to October 2015.

Relevant clinical and laboratory data was collected with reference to age at the start of transfusions, total number of transfusions received and splenectomy status. Antibodies screening, antibody identification, and cross matching was done on all patient samples included in the study.

### **Screening for alloantibodies**

Screening for alloantibodies is routinely done in our set up and if it is positive samples are preserved at -40°C and identification is done depending on the availability of identification cells. Blood samples were obtained in EDTA vacutainers for detection of red cell alloantibodies and the serum or plasma was separated as per manufacturer's directions. Antibody screening was done by using Immucor Panoscreen three vial set and if screening came out to be positive antibody identification was then done by using Immucor Panocell-10.

Quality control of saline, screening cells was performed every time samples were screened for irregular antibodies. These tests were performed in accordance

### **Identification of antibodies**

Antibody identification was performed by using Immucor antibody identification RBC panel cells (Panocell-10). The procedure was performed in accordance to the manufacturer's instructions.

### **Ethical clearance**

The study was approved by the Institutional Ethics Committee of our Hospital.

### **Statistical analysis**

Computer software Microsoft excel for windows was used in analysing the data. All the information was compiled, tabulated and analysed from the input gathered from the patients involved in the study. Descriptive statistics and Fisher's exact test was used to calculate the P value, wherever necessary.

## **RESULTS**

### **Distribution with respect to age**

There were a total no. of 146 thalassemia major patients included in the study, who received regular moderate transfusion regime during the one year period of our study. The patients included in the study had ages ranging between 2 year to 32 years. Mean age was 11.02 years whereas median age was 10 years. Age wise distribution is depicted in Table 1.

All the patients were divided according to their age into 6 subgroups of class interval 5 i.e.; <5 years, 5-10 years, 10-15 years, 15-20 years, 20-25 years, >25 years.

Maximum number of 51 patients constituting 34% of the total patients were in age group 5-10 years whereas in age group >25 years there were only 5 patients constituting 3.45% of the total patients. Distribution with respect to age is depicted in Table 1.

**Distribution with respect to sex**

The distribution of patients with respect to sex is shown in Table 2. Total number of females in the study were 57 accounting for 39% of all subjects whereas no. of males were 89 accounting for 61% of the subjects. The female: male ratio was 1:1.56.

**Distribution based on number of transfusions**

Number of transfusions ranged from a minimum of 15 to a maximum of 792 in one patient. Mean number of transfusions received were 180. Maximum patients (45%) had received less than 100 transfusions at the time of study. A total of 2950 transfusions were given during the study period. Mean number of transfusions per patient per year was 20.20. Distribution of patients according to the no. of transfusions received is depicted in Table 3.

**Table 1: Distribution with respect to age.**

Age (years)	No. of patients	Percentage (%)
0-5	31	21.23
5-10	51	34.93
10-15	30	20.54
15-20	19	13.01
20-25	10	6.84
>25	5	3.42

**Table 2: Distribution with respect to sex.**

Sex	No. of patients	Percentage (%)
Females	57	39
Males	89	61

**Association of autoantibodies with splenectomy**

The association of splenectomy with presence of autoantibodies was also documented. Out of a total 7 splenectomized patients 4 patients developed autoantibodies after splenectomy.

**Table 3: Distribution based on number of transfusions.**

No. of transfusion	No. of patients	Percentage (%)
0-100	67	45.9
101-200	34	23.3
201-300	18	12.3
301-400	12	8.2
401-500	5	4.1
>500	10	6.8

**Distribution based on blood group**

Distribution based on blood group type is depicted in Table 4. There were patients of all major blood group types.

Maximum no. of 33% patients were of B positive blood group whereas only 1 patient had AB negative blood group.

**Distribution based on RH factor**

Distribution based on Rh factor type is depicted in Table 5. There were a total of 131 Rh positive patients constituting 89.8% of the total patients whereas 15 patients constituting 10.2% of total patients had Rh negative blood group.

**Table 4: Distribution based on blood group.**

Blood group	No. of patients	Percentage (%)
A+ve	32	22
B+ve	48	33
AB+ve	19	13
O+ve	32	22
A-ve	4	3
B-ve	2	1
AB-ve	1	0.7
O-ve	8	5

**Table 5: Distribution based on RH factor.**

RH factor	No. of patients
RH positive	131
RH negative	15

**Table 6: Distribution of alloantibodies.**

Total no. of patients	Alloantibody at the start of study	Alloantibody at the end of study
146	8	10

**Table 7: Distribution based on alloimmunization.**

No. of patients (at the start of the study)	No. of patients (at the end of the study)		
	AlloAb negative	AlloAb positive	Total
AlloAb negative	131	7	138
AlloAb positive	5	3	8
Total	136	10	146

**Distribution based on alloimmunization**

Antibody screening was carried out in all patients and this was followed by antibody identification in those patients who had tested positive in screening. At the start of the study there were a total of 8 patients who tested positive for various alloantibodies developed due to recurrent transfusions in the past.

Similarly, antibody screening revealed that there were 10 patients who were positive for alloantibodies at the end of the study. By applying McNamar test, p value was 0.56

which is not significant. The screening results are shown in Table 6 and 7.

#### **Association of alloimmunization with age at first transfusion and number of transfusions**

Of the 64 patients who received their first transfusion before 1 year of age 2(3%) patients developed alloantibodies whereas out of a total of 78 patients who received first transfusion between 1-5 years of age 11 (14%) patients developed alloantibodies.

Only 4 patients had their first transfusion after 5 years of age of which 2 (50%) developed alloantibodies. The association of age at first transfusion with development of alloimmunization is shown in Table 8.

The alloimmunization rate was seen higher in those who received 12 transfusions (8.82%) as compared to those who received up to 12 transfusions (0%). By applying Fisher exact test, p value of 0.01 was calculated which is statistically significant.

#### **Distribution based on type of alloantibodies**

Of the 8 patients who tested positive for alloantibodies in screening, antibody identification revealed that 3 patients had more than one antibody subtype. Anti-E was the commonest antibody found in 4 (50%) patients. Similarly, at the end of study, antibody screening and then identification revealed presence of antibodies in 10 patients.

Only 1 patient had more than one antibody subtype. Anti E was again the commonest antibody found in 5 (50%) patients. The distribution of types of alloantibodies at the start and at the end of the study are shown in Table 9.

#### **Distribution based on presence of autoantibodies**

Autoantibody screening was carried out in all patients by Direct Coomb's test. Of the total 146 patients only 21 tested positive whereas the rest 125 patients tested negative. Of the 21 positives, only 3 patients had warm agglutinins whereas 18 patients had cold agglutinins. The results of autoantibody screening are shown in Table 10.

**Table 8: Association of alloimmunization with age at first transfusion.**

Age at the start of transfusion (years)	Total no. of patients	No. of patients with alloantibody	Percentage (%)
<1	64	2	3
1-5	78	11	14
>5	4	2	50

The crude Odds ratio (95%CI) was 9.56 (1.97-46.4%) and Chi square 10.92 (p<0.001, highly significant) signifying

that splenectomized patients have approximately 10 times more risk of developing autoantibodies than non-splenectomized patients, as shown in Table 11.

**Table 9: Distribution based on type of alloantibodies.**

Type of antibody	No. of patients at the start of study	No. of patients at the end of study
Anti C	1	1
Anti D	2	2
Anti E	4	5
Anti K	2	3
Anti S	1	0
Anti c	1	0

**Table 10: Distribution based on presence of autoantibodies.**

Total patients	DCT negative	DCT positive	
		21 (14%)	
146	125 (86%)	Warm Ab	3 (2%)
		Cold Ab	18 (12%)

**Table 11: Association of autoantibodies with splenectomy.**

Variables	Auto-antibody present	Auto-antibody absent	Total	Odds ratio
Non-splenectomised	17	122	139	9.56 (1.97-46.4)
Splenectomized	4	3	7	
Total	21	125	146	

## **DISCUSSION**

Out of the total 146 patients, there were a total of 89 (57%) male patients and 57(43%) female patients. The female: male ratio was 1:1.56. This male preponderance was similar to other the findings of other studies. Sadeghian et al reported similar male preponderance with 59% males and 40% females.<sup>9</sup> Bilwan et al reported a female: male ratio 1:1.2 and Mansour et al reported female: male ratio of 1:1.25.<sup>10,11</sup>

The patients included in the study were in the age range of 2 to 32 years with mean age of 10.2 years and median age of 11 years. Sadeghian et al reported age range of 8 months to 38 years and mean age of 14.42 years.<sup>9</sup> This was also seen in the studies of Mansour et al who found median age of 13 years and Belhoul et al where mean age was 15.4 years.<sup>11,12</sup> In our study 21 percent of patients were less than 5 years of age, 56 percent between 5 to 15 years, 23 percent over 15 years of age. In a similar study, Sirchia et al in 1985 found that 18 percent of the patients were under 6 years of age, 63 percent between 6 and 15, and 19 percent

over 15.<sup>7</sup> The increasing mean age and upper age of the patients is indicative of the prolongation of survival in these patients over past few decades. In our study there were a total of 90% Rh positive patients and 10% Rh negative patients. The distribution of blood groups was A 36 (24.7%), B 50 (34.2%), AB 20 (13.7%), and O 40 (27.4%) patients. Haslina et al reported distribution of blood group as A (20.7%), B (37.9%), AB (13.8%), and O (27.6%).<sup>13</sup>

### **Alloimmunization**

Antibody screening was carried out using 3 cell panel in all patients both at the start and at the end of the study. At the start of the study there were a total of 8 (5.5%) patients who tested positive for various alloantibodies developed due to recurrent transfusions in the past. Similarly, antibody screening revealed that there were 10 (6.8%) patients who were positive for alloantibodies at the end of the study. There was no significant change in the prevalence of antibodies during the course of our study ( $p = 0.56$ ). The frequency of alloimmunization has been reported from as low as 2.87% to as high as 30% in various studies. Vichinsky et al in 2014 published a report from the Centers for Disease Control and Prevention titled Transfusion complications in thalassemia patients where 407 thalassemia patients were enrolled.<sup>14</sup> In their report 19% (68/365) of all transfused patients had alloantibodies. Twenty-three percent of chronically transfused patients were alloimmunized, compared to 13% of the intermittently transfused ( $p = 0.30$ ). Ameen et al reported an incidence of alloimmunization of 30%.<sup>15</sup> In a similar study in Sadeghian et al in 2009 reported alloimmunization in only 2.87% patients.<sup>9</sup> Pahuja et al in 2010 carried out a similar study in north India and reported an incidence of 3.79%.<sup>16</sup> In another Indian study by Dhawan et al the rate of alloimmunization was 5.64%.<sup>17</sup> This low rate of alloimmunization in our study and as reported in other studies may be due to homogeneity of RBC antigens between the blood donors and recipients sharing same ethnicity as most of our patients and blood donor population is from Jammu (Dhawan et al).<sup>17</sup>

The number of patients who developed alloantibodies was also influenced by the age at first transfusion in our study. While only 3% patients who had their first transfusion before 1 year of age developed alloantibodies, a significant 14% patients who had their first transfusion between 1-5 years and 50% patients who had their first transfusion after 5 years of age developed alloantibodies. In the study of Vichinsky et al the alloimmunization rate in children who began transfusion before 1 year of age was 11% compared to 27% who began transfusion after 1 year of age.<sup>14</sup> This can be explained by the fact that the patients who receive their first transfusion at an earlier age develop immune tolerance and hence are less likely to develop alloimmunization (Spanos et al, Rosse et al, Calderone et al, 2009).<sup>18-20</sup> In our study alloimmunization was found in 28.5% of splenectomized patients and 5.7% of non-splenectomized patients ( $p < 0.005$ ). In the study of

Vichinsky et al, alloimmunization was found in 31% of splenectomized patients vs. 11% of non-splenectomized patients.<sup>14</sup> This reconfirms the fact that absence of spleen also increases chances of alloimmunization (Thompson et al).<sup>21</sup> The reason could be due to increased circulation of antigens in the absence of spleen and hence causing increased alloimmunization rates (Pattanapanyasat et al, Westerman et al).<sup>22,23</sup> In this study we found that earliest development of antibodies was found after transfusion of 12 units of packed cells. A significant association between alloimmunization and number of transfusions was observed ( $p \text{ value} < 0.05$ ). Spons et al reported earliest sensitization after approximately 10 transfusions in thalassemic patients.

The patients who tested positive on screening had antibody identification carried out on 11 cell panel. Of the 8 patients who tested positive at the start of the study 3 (37.5%) patients had more than one antibody subtype. Anti E was the commonest antibody found in 4 (50%) patients. Anti C, anti D, anti K, anti S and anti C were also identified. At the end of study out of 10 only 1 (10%) patient had more than one antibody subtype. Anti E was again the commonest antibody found in 5 (50%) patients. Other types identified were anti C, anti D and anti K. In the report of Vichinsky et al forty-seven percent of alloimmunized patients had multiple antibodies: anti E (29%), anti K (17%), or anti C (12%) were identified in most of these patients.<sup>14</sup> In a similar study, Sadeghian et al found most common alloantibody was anti D (88.88%) followed by anti C (33.33%) and anti E (11.11%).<sup>9</sup> In their report 3 patients (33.33%) had two different alloantibodies. Alloimmunization hence remains a concerning issue in all populations of thalassemia patients receiving multiple transfusions. Studies have been carried that show that Alloimmunization can be reduced by Limited donor exposure programs (El-Danasoury et al) or extended red cell matching (Williams et al).<sup>24,25</sup> In our study red cell alloantibody disappeared in one patient when he was transfused phenotype matched i.e.; antigen negative blood over the period of our study. Thus, regular screening of all patients for the presence of alloantibodies and the already alloimmunized patients to check for disappearance of older alloantibodies or appearance of newer alloantibodies needs to be carried out so as to enable the implementation of cost effective extended red cell phenotype matching programs.

### **Prevalence of autoimmunization**

Autoantibody screening was carried out in all patients by Direct Coomb's test. Of the total 146 patients 21 (14.3%) patients tested positive whereas the rest 125 patients tested negative. Of the 21 (14.3%) positive only 3 (2%) patients had Warm agglutinins whereas 18 (12.3%) patients had cold agglutinins. Vichinsky et al reported autoantibodies occurrence in 6.5% of patients; chronically transfused and intermittently transfused patients had a similar risk (6.4% vs. 6.9%).<sup>14</sup> Haslina et al in a similar study found autoantibodies in only 1.7% of patients while Ameen et al



found autoantibodies in 11% patients.<sup>13,15</sup> There was a high rate of autoantibody formation in splenectomized patients in our study. Out of the total 7 patients who had undergone splenectomy 4 (57.14%) patients developed autoantibodies. This high rate of autoimmunization has been reported in other studies (Danasoury et al, Leiby et al).<sup>24,26</sup> The high rates of autoantibody formation in splenectomized patients could be due to the fact that blood transfusion is associated with lymphocytosis, elevated levels of serum immunoglobulins, immune complexes and cells expressing surface immunoglobulins which remain unchecked in the absence of spleen (Leiby et al, Mali et al 2010, Tonnetti et al 2009).<sup>26-28</sup> All identified alloantibodies belonged to Rh system [i.e.; anti E, in 5 patients (50%), anti C and anti D in one patient each (10%) and Kell system (anti K, in three patients (30%)).

One of the limitation of our study was that we had not studied the effect of leucoreduced and use of bed side filters used by some thalassemic patients on alloimmunization. We also recommend obtaining an RBC antigen phenotype on all thalassemia patients before the start of transfusion support and if feasible providing leuco-reduced blood to all.

## CONCLUSION

Due to high incidence of anti Rh system (70%) and anti K (30%) antibodies in our study population, it is advisable to phenotype patients and donors and matched red cell units for at least Rh blood group system and Kell blood group system antigens in addition to ABO and D antigen should be provided. Antigen-matched transfusions should effectively prevent alloimmunization for thalassemia patients who have a lifelong, transfusion-dependent disease.

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