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Original Research Article

Red cell alloimmunization in repeatedly transfused children with beta thalassemia major

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ABSTRACT

Background: The development of anti-red blood cell alloantibodies remains a major problem in thalassemia major patients. We studied the frequency of red blood cell (RBC) allo-immunization among Beta thalassemia major patients who received regular transfusions at our center and analyzed the factors, which may be responsible for development of these antibodies.
Methods: An observational study was conducted in department of Pediatric Medicine, SMS Medical College, Jaipur. A total of 150 patients of Beta Thalassemia major who already received multiple transfusions were randomly selected and screening of Red Cell Alloantibodies was done by using SPRCA (solid phase red cell adhesion) method during May 2015 to April 2016. Statistical analysis was done using computer software (SPSS version 20 and primer). The qualitative data were expressed in proportion and percentages and the quantitative data expressed as mean and standard deviations. The difference in proportion was analysed by using chi-square test and the difference in means were analysed by using student t- Test. Significance level for tests were determined as 95% ($P < 0.05$).
Results: Total 150 cases were included. Male female ratio was 1.63:1, 10 cases (6.67%) were positive for alloantibodies. Among these 10 positive cases, 2 had positive family history and 3 had history of splenectomy. In allo-immunised cases mean age, mean age at first transfusion and total number of transfusions were significantly higher in comparison to non-allo-immunized cases.
Conclusions: If patient has red cell alloantibody on regular interval screening then the antibody identification should be performed and corresponding antigen negative blood transfusion is strongly recommended in transfusion dependent thalassemia patients.

Keywords: Alloantibodies, Multiple transfusions, Thalassemia major

INTRODUCTION

Thalassemia is an autosomal recessive blood disorder characterized by weakening and destruction of red blood cells due to variant or missing genes that affects the process of haemoglobin formation. The homozygous state, Thalassemia Major, results in a severe anemia and often death before puberty. The heterozygous state, Thalassemia minor, is less severe and may be asymptomatic with little or no anemia. Depending on the affected haemoglobin chain, Thalassemia can be characterized as alpha, beta or delta Thalassemia. The recommended treatment for β-Thalassemia Major is regular blood transfusion every 3-4 weeks, with a goal to correct the anemia to suppress the hyperactive erythropoiesis and to inhibit the excessive gastro-intestinal iron absorption. The regular blood transfusion regimen is confronted with numerous complications.[1]

In almost every patient, the transfusion requirement slowly increases over the years. Various factors which

contribute towards this increased requirement include development of hypersplenism, alloimmunization against various blood group antigens, chronic infections, folate deficiency (if not continually corrected by regular life time folate intake), progressive bone marrow fibrosis as a result of toxic effect of free elemental iron, aplastic crises and hemolytic crises etc.

The distribution of various blood groups antigens varies amongst individuals in any given population.[2] Therefore, there is a variable degree of disparity amongst the donors and the recipient regarding the group systems other than 'ABO' and Rh 'D', which are not tested before routine transfusions. As a result, at some stage during the transfusion management, this disparity of blood group systems can lead to alloimmunization and therefore elaboration of antibodies against the immunogenic antigen system.[3] So, the present study was undertaken to determine the sero-prevalance of anti-red cell alloantibodies in Beta Thalassemia Major patients who received multiple transfusions.

METHODS

It was a hospital based observational study carried out in department of pediatric medicine, SMS Medical College, Jaipur from May 2015 to April 2016. Permission from ethical committee of S.M.S. Medical College, Jaipur was taken prior to the study. Total 150 patients were randomly selected and included in study with 95% confidence interval and 10% allowable error. Screening of red cell Alloantibodies by SPRCA (solid phase red cell adhesion) using machine IMMUCOR was done.

Thalassemia major patients with multiple blood transfusions attending the department were considered for study. Consent was taken in all the cases. Clinical data were entered into a preformed proforma.

Statistical analyses were done using computer software (SPSS version 20 and primer). The qualitative data were expressed in proportion and percentages and the quantitative data expressed as mean and standard deviations. The difference in proportion was analysed by using chi square test and the difference in means were analysed by using student t Test. Significance level for tests were determined as 95% ($P < 0.05$).

RESULTS

In the study 150 Beta Thalassemia Major patients were taken, in which 93 were males (62%), 57 females (38%) and M: F ratio was 1.63:1.

Ten patients (6.67%) developed alloantibodies. There was no statistically significant gender wise difference for the development of allo-antibodies. Patients included in the study ranged from 1 to 17 years in age. 57 Patients (38%) were below 5 year of age. 11 children had history of prior splenectomy. 72.6% patients got their first blood transfusion below 1 year of age (Table 1).

Table 1: Characteristics of patients enrolled in the study.

Parameters	Alloimmunised (n = 10)	Non alloimmunised (n = 140)	Total (150)
Gender			
Male (93)	3 (30%)	90 (64.28%)	93 (62%)
Female (57)	7 (70%)	50 (35.71%)	57 (38%)
Age			
<5 years	1 (10%)	56 (40%)	57 (38%)
5 to 10 years	3 (30%)	39 (27.8%)	42 (28%)
10 to 15 years	3 (30%)	39 (27.8%)	42 (28%)
>15 years	3 (30%)	6 (4.2%)	90 (6%)
Splenectomy			
No	7 (70%)	132 (94.28%)	139 (92.66%)
Yes	3 (30%)	8 (5.71%)	11 (7.33%)
Age at first transfusion			
<6 months	1 (10%)	9 (6.428%)	10 (6.66%)
6 - 12 months	1 (10%)	98 (70%)	99 (66%)
1 - 3 years	3 (30%)	24 (17.14%)	27 (18%)
3 - 5 years	5 (50%)	9 (6.428%)	14 (9.33%)

The mean age of the non-alloimmunized and alloimmunized patients was 7.34± 3.95 years and 11.90± 4.28 years respectively.

Significantly higher mean was observed among the alloimmunised as compared to non-alloimmunised ($p<0.001$). Mean age at first transfusion was significantly higher in alloimmunized (27.40 months) than non-

immunized patients (12.09 months). Total number of transfusions received by alloimmunized patients (164.30±81.85 versus 93.28±65.65) was significantly higher (Table 2). Among 10 positive alloimmunized cases, 2 had positive family history and 3 had history of splenectomy (Table 3).

Table 2: Frequency of alloantibodies in patient's population in relation to mean age of patient, age at first transfusion and total number of transfusions.

Parameter	Alloimmunised (n = 10)	Non Alloimmunised (n = 140)	p-value
Mean age±SD (years)	11.900±4.29	7.341±3.95	0.000
Mean age±SD at first blood transfusion (months)	27.40±21.60	12.09±10.71	0.000
Total no. of blood transfusions±SD	164.30±81.85	93.28±65.65	0.001

Table 3: Details of patients who developed alloantibodies.

Sex	Age (years)	Age at first transfusion (months)	Blood group	Family history	History of splenectomy	No of blood transfusions
F	17	26	AB+	No	Yes	272
F	8.5	8	B+	No	No	100
F	4	4	O+	No	No	38
F	13	14	B+	Yes	No	187
F	16	30	B+	No	Yes	249
F	15	54	A+	No	No	231
F	13	46	O-	No	No	113
M	8	24	O+	Yes	No	99
M	9	26	AB+	No	No	109
M	15.5	42	AB+	No	Yes	245

DISCUSSION

The factors affecting alloimmunization are complex and involved 3 main contributing elements, the RBC antigenic difference between the donor and the recipient, the recipient's immune status and immunomodulatory effects of allogeneic blood transfusion.[4] In the study total 150 Beta Thalassemia Major patients were taken, in which 93 were males (62%), 57 females (38%) and M: F ratio being 1.63:1. Patients included in the study ranged from 1 to 17 years in age. The mean age of the studied non-alloimmunised and alloimmunised patients were 7.341±3.9516 and 11.90±4.28 years respectively. Significantly higher mean was observed among the alloimmunised as compared to non-alloimmunised. For the red cell alloantibodies screening, commercially prepared three red cell panels were used. The overall incidence of RBC Alloimmunization was low, which was 6.67%. This low incidence of alloimmunization was consistent with the study by Choudhary et al and Pradhan et al, who noted alloimmunization between 5 to 8 %.[5, 6] A study from Italy reported 5.2 % alloimmunization.[7] A low rate of alloimmunization may be expected when there is homogeneity of red cell antigens between the blood donors and the recipients.

Michail et al reported 23.43% rate of alloimmunization in those who received blood matched for ABO and Rhesus antigen only (unmatched group) and 14.28% in those who received blood matched for ABO, Rhesus and Kell (better matched group).[8] Alloimmunization rate was reported high in studies from Greece and Kuwait, 22 and 30% respectively.[4,9] Higher alloimmunization rates might be due to the heterogeneity of the population living in Greece and Kuwait and mismatched RBC phenotype between donor and recipients.

Various factors affect the rate of alloimmunzation, such as racial factors, disparity between antigenic frequency of donors and the recipients, gender, age at first transfusion, total no. of blood transfusion, splenectomy etc. Out of total 10 alloimmunized patients, three were males and seven females. No statistically significant association was found between gender and alloimmunisation. Many Studies also showed that gender was not a significant factor in the development of alloimmunization.[9-11] However, Reisner et al reported a significant association between alloimmunization and gender, especially in developing countries, as they found anemia and pregnancy are important risk factor for alloimmunization.[12]

In this study, rate of alloimmunization was lower in patients who received their first transfusion at <3 years of age (40%). The mean age (months) at first transfusion in the studied non-alloimmunised and alloimmunised patients were 12.09±10.71 and 27.40± 21.60months respectively. The difference was statistically significant (P<0.001). Spanos T et al showed that Alloimmunization appeared considerably lower in patients in whom blood

transfusion was started before the age of 3 years than in those in whom it was started at later age (20.9 vs. 47.5%).[13] Alloimmunization risk was significantly lower in hemoglobinopathy patients who started transfusion therapy at a very young age (<3 years) compared with those who started later in life, where an immature immune system and some form of the acquired immune tolerance to allogeneic RBC antigens is held responsible for the reduced alloimmunization risk.

This study reported higher number of total blood transfusion in alloimmunized patients. The mean no. of blood transfusion in the non-alloimmunised and alloimmunised patients was 93.28±65.65 and 164.30±81.847 respectively.

Significantly higher mean was observed among the alloimmunised as compared to non-alloimmunized. Few studies observed strong correlation between the number of blood units transfused and alloantibody formation.[7,14] While other studies found no relationship between the number of transfusions and alloimmunization rate.[8,15] Spanos T et al observed that the relation between the number of units of blood transfused and antibody formation is unknown in Thalassemia major but it is an important factor for increased alloimmunization.[13]

Splenectomy is also considered as a risk factor for alloimmunization. There was statistically significant difference between splenectomized and nonsplenectomized patients as regard to alloimmunization rate (27.27% versus 5.0%, p = 0.027). This observation is similar to the study of Hussein et al. who reported a higher rate of alloimmunization in splenectomized patients.[16] However, some studies reported an insignificant association between splenectomy and alloimmunization rate in thalassemia patients.[7,15] These conflicting results may be related to various factors including RBC transfusion burden, timing of initial RBC antigen exposure (presplenectomy versus postsplenectomy), and the life span of transfused RBC.

In this study only alloantibody screening was done. We did not identify specific alloantibodies if it is required then extended phenotyping is must with commercial 11 red cell panel cells.

CONCLUSION

Early institution of antigen matched blood (for Rh and Kell antigen) transfusion therapy after diagnosis decreases alloimmunization in Beta Thalassemia major patients.

If patient has red cell alloantibody on regular interval screening then the antibody identification should be performed and corresponding antigen negative blood transfusion is strongly recommended in transfusion dependent thalassemia patients.

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