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Comparative study of alloimmunization against red cell antigens in sickle cell disease & thalassaemia major patients on regular red cell transfusion

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***Background & objectives*: Sickle cell disease (SCD) patients require red cell transfusion during different clinical complications of the disease. Such patients are at a high risk for developing alloantibody against red cell antigens. From India, there are limited data available on alloantibody formation in multiply transfused SCD patients. The present study was thus undertaken to fill up this lacunae by looking at the development of red cell alloantibodies in SCD and β-thalassaemia patients on regular transfusion.**

***Methods*: All sickle cell disease patients undergoing red cell transfusion between 2008 and 2016, were included. During this period, a large number of β-thalassaemia major patients also underwent regular red cell transfusion. These thalassaemia patients were also included to compare the tendency of antibody formation between SCD and β-thalassaemia major patients. All patients before regular transfusion were regularly assessed for the development of red cell antibody. Red cell antigen, antibody screen crossmatch and antibody identification were done using the standard technique.**

***Results*: A total of 138 patients with SCD aged between 4 and 53 yr (mean 17.6 yr) consisting of 83 males and 55 females (male:female, 1.5:1) along with 333 transfusion-dependent β-thalassaemia patients were studied. Over the last eight years, 15 patients with SCD and four patients with thalassaemia developed alloantibody (P<0.001). Antibody specificity of their alloantibodies was against Rhc, RhE, Kell, Fy^a and Fy^b only. Sickle cell disease patients with and without alloantibody required on the average 11.8 and 8.6 units of red cell concentrate, respectively (P<0.05).**

***Interpretation & conclusions*: About 11 per cent of the transfused sickle cells patients developed alloantibodies. The antibody specificity was restricted to Rh, Kell and Duffy blood group systems. Extended antigen matching involving Rh, Kell and Duffy antigens may prevent alloantibody in such patients.**

Key words Alloantiboy - antibody specificity - multitransfused patients - red cell transfusion - sickle cell disease - thalassaemia

Patients, who get multiple red cell transfusions develop alloantibodies against one or many red cell antigens[1,2]. There are many modifiers for the development of alloantibodies following red cell transfusion and some of them can be summarized as follows: (*i*) absence of a given red cell antigen in the recipient but its extensive presence in donor population, (*ii*) antigenicity of the given antigen against which

alloantibody is formed, for example, RhD and Kell are strongly antigenic. This also includes the prevalence of red cell antigen mismatch between donor and recipient population, (*iii*) nature of underlying disease for which the transfusion is initiated, (*iv*) number of red cell units transfused, (*v*) leucodepleted or non-leucodepleted red cells (this is important for the development of anti-HLA antibody which may alro altect red cell survival), (*vi*) the racial differences in blood group antigen distribution between donor and recipient population, (*vii*) age at which the transfusion is initiated, (*viii*) average lifespan of the patient with the disease, (*ix*) recipient's inflammatory state at the time of transfusion and (*x*) concomitant medication, immune suppression which may be given alongside red cell transfusion, (*e.g*., chemotherapy, immunosuppressants, transfusion of IV Ig and splenectomy)[3]. Many complications of sickle cell disease (SCD) require red cell transfusion, and therefore a large proportion of these patients require regular red cell transfusion or exchange transfusion. India is home to estimated 1.5×10^5 sickle cell disease patients[4]. There is no limited information from India, on the occurrence of red cell alloantibodies in these patients except a few including case reports[5,6]. The present retrospective study was an attempt to address this question by assessing the occurrence of red cell alloantibodies in patients with SCD on regular transfusion in a tertiary care centre in Gujarat, India.

Material & Methods

Consecutive patients having sickle cell disease, who attended regular transfusion service of Surat Raktadan Kendra and Research Centre, Surat, India, between 2008 and 2016, were included in this study. For comparison, transfusion-dependent thalassaemia major patients were also included in this study. The records of these patients were evaluated for any adverse transfusion reaction.

Investigations: All patients were investigated just before the next red-cell transfusion. Standard immuno-haematological techniques as described in the American Association of Blood Banks (AABB) manual were followed[7], along with the instructions in the packet insert of individual cell panels used in this study. Since DiaMed (DiaMed AG, Switzerland) 3-cell panel may not include all the red-cell antigens pertinent to the Indian population, a locally made (Tulip Diagnostics, India) 3-red cell panel was also used for screening the atypical antibodies. The patients' ABO, RhD antigen status, antibody screening was done by DiaMed 3-cell panel and a 3-cell panel by Tulip diagnostics using gel technique. In addition to the above, a LISS (low ionic strength solution)-indirect Coombs test, a standard cross matching and a DiaMed 11-cell panel was used for the identification of positive a typical antibodies[7].

The study was approved by the Institutional Review Board (SRKRC/RP/4/2017). As it was a retrospective data analysis and screening for alloantibody against important red cell antigens and the identification of antigen(s) against which the antibodies were formed was a requirement for safe transfusion, the patients were not identified and the consent forms from individual patients were not obtained.

Transfusion: All patients on regular transfusion received Coombs cross-matched red cells and in case of positive antibody screen, antigen-negative red cells which were thrice saline washed. At this transfusion centre, extended phenotype matched red cell transfusion was not routinely practiced.

Statistical analysis: For statistical analysis of data λ^2 test with Yates correction was used for non-parametric data and Student's (unpaired) *t* test for parametric data.

Results

A total of 138 patients with SCD received between 1 and 61 units of packed red cell transfusion (total 1234 units with a mean of 8.9 units/patient) over eight years. During the same period, 333 β-thalassaemia major patients received on the average 246 ml/kg of packed red cell/kg/year (mean 17.6 units of packed red cells/patient/yr). The age group of sickle cell disease patients was much broader (4-53 yr) with a male:female ratio of 1.5:1 whereas for transfusion-dependent β-thalassaemia major patients the age range was narrower between 4 and 26 yr with a male:female ratio of 1.3:1. The amount of red cell transfusion in thalassaemia patients was 15-16 times more than that of SCD patients. Of the 138 patients with sickle cell disease, 15 (11%) developed alloantibodies compared to 4 of 333 (1.2%) thalassaemia major patients ($P<0.001$). The number of transfusions given to alloimmunized SCD patients (11.8±16.6 units) when compared to those who did not get alloimmunized (8.6±15.26 units) were not significantly different. There was no difference in reactivity between DiaMed and Tulip screening red cells for the patients screened.

Of the 15 patients with SCD who developed alloantibodies, 12 developed alloantibody on

Table I. Alloantibodies in transfused sickle cell disease and β-thalassaemia patients

SI. No.	Age (yr)	Sex	Number of past transfusion	Antibody specificity
1	12	Male	38	Anti K
2	34	Female	4 (multipara)	Anti E
3	14	Male	20	Anti c
4	28	Male	2	Anti c
5	14	Female	1	Anti E
6	14	Male	10	Anti E
7	20	Male	7	Anti c
8	30	Female	1 (Para 1)	Anti E
9	15	Female	4	Anti Fy^b
10	12	Female	6	Anti Fy^a
11	47	Male	5	Anti c
12	35	Male	2	Anti c
13	53	Female	10 (multipara)	Anti c
14	7	Male	61	Anti E
15	17	Male	6	Anti c
Total	Mean 23.4 (7-53)	Male: female=9:6	177 (11.8±16.6)	Anti c=7 Anti E=5 Anti Jk^a, Jk^b, K=1 each
Total 123 (no alloantibody)	16.96 (4-44)	Male: female=15:1	1057 (8.6±15.26)	
Transfusion-dependent β-thalassaemia (n=333)	11.3 (4-26)	Male: female=1.3:1	246 ml/kg/yr (150-430 ml/kg/yr)	4 developed alloantibody Anti c-2 Anti E-2

χ^2 test with Yates correction. $P<0.001$ between number of β-thalassaemia patients versus sickle cell disease patients developing alloantibody. Number of units of red cells transfused: β-thalassaemia versus sickle cell disease; Students *t* test $P<0.001$

receiving 10 or less number of red cell units. For both the SCD as well as thalassaemia major patients, Rhc and E were the most common antigens involved, additional Kell, FY^a and FY^b (1 patient each) (Table I) antigens were involved in SCD patients receiving multiple transfusion. Number of red cell units received by thalassaemia patients was significantly more ($P<0.001$) compared to that of SCD patients. Comparison of alloantibody formation in multitransfused SCD patients in the global studies is shown in Table II[2,8-16]. The comparison of alloantibody generation in thalassaemia patients in the present study with other studies on multitrans fused patients in India is presented in Table III[17-31].

Discussion

Several studies have recorded the development of alloantibodies in hospitalized patients and multitransfused patients with thalassaemia, and other conditions[5,17-31] from India and the prevalence of such antibodies varied widely between 0.49 and 18.8 per cent. One study compared the transfusion practice for sickle cell disease patients between a centre in India and a sickle cell management centre in Jamaica[32], though no assessment of alloantibody formation in Indian patients was made in that study. Majority of the data of alloantibody formation from Western countries in SCD patients receiving transfusion showed up to 76 per cent alloimmunization, and the prevalence across the world varied between 2.6 per cent in Jamaica to 65 per cent for ABO, RhD only matched red cells in Kuwait and 76 per cent in Jamaican sickle cell disease patients taking transfusion in the UK[11,14,33]. Table II provides the broad range of such data across the world. The increased prevalence of alloantibodies in transfused sickle cell disease patients in Western countries have largely been explained on the basis of racial mismatch of major red cell antigen system between blood donating Caucasian population and SCD patients from African,

Table II. Global literature on alloantibodies in sickle cell disease patients receiving transfusion

Author	Number of patients studied	Prevalence of antibody (%)	Specificity if known
Rosse *et al*, 1990[2]	1814	18.6	C, E, Kell, Le^a, Le^b
Natukunda *et al*, 2010[8]	428	6.1	Rh and MNs
Castro *et al*, 2002[9]	351	39.03	Ce, Ee, Kell and Rh.D
Bashawri 2007[10]	350	13.7	RhE C Kell and Non-specific
Sarnaik *et al*, 1986[11]	245	7.75	RhD, Kell Le^a/Le^b
Ameen *et al*, 2009[12]	233 (110 ABO/D matched. 123 Extended phenotype matched)	6.5 23.6	Rh and Kell
Olujohungbe *et al*, 2001[13]	190 (Jamaica) 37 (Manchester)	2.6 76	Rh and Kell Jk
Present study	138	10.86	c E, Kell, Jk^a, Jk^b
Vichinsky *et al*, 1990[14]	107	30	Kell, E, C, Jk^b
Moreira *et al*, 1996[15]	85	12.9	Rh and Kell
Aygun *et al*, 2002[16]	N/A	47 (Adult)	C E D Kell

Table III. Alloantibodies produced by red cell transfusion against diverse conditions in India where donor and recipient populations were similar

Author	Number of patients studied	Diagnosis	Prevalence (%)	Specificity if known
Jolly *et al*, 1992[17]	251	Thalassaemia	15.5	Rh K
Shukla *et al*, 1999[18]	81	CRF	9.8	Rh Kell, Fy M N and S
Pradhan *et al*, 2001[19]	100	Thalassaemia	8	D C Fy N
Thakral *et al*, 2008[20]	531	Multitransfused patients of diverse aetiologies	3.4	E, E, M, D, Le^a
Pahuja *et al*, 2010[21]	211	Thalassaemia	3.79	E, K, D, Kp, Ce, Jk^a
Gupta *et al*, 2011[22]	116	Thalassaemia	9.48	E, K, Kp^a C^w
Chaudhari *et al*, 2011[23]	32	Thalassaemia	18.8	E c
Makroo *et al*, 2013[24]	3006	CRF, liver dis. Chronic anaemia and thalassaemia	5.6	Rh C and E
Makroo *et al*, 2013[24]	462	Thalassaemia	4.1	Kell
Makroo *et al*, 2014[25]	49077	Total hospital population receiving at least one transfusion	0.49	D, E, Kell
Dhawan *et al*, 2014[26]	319	Thalassaemia	5.64	EDC Jk^a
Elhence *et al*, 2014[27]	280	Thalassaemia	8.6	E, K, e
Jain *et al*, 2014[28]	96	Thalassaemia	5.21	E K
Datta *et al*, 2015[29]	500	Thalassaemia	5.6	
Dhar *et al*, 2015[30]	49	Surgical Onco	2.5	E, Fy, Le^a, Le^b
Jain *et al*, 2016[31]	301	Thalassaemia	3.6	E, D, K
Present study	333	Thalassaemia	1.2	E, c

CRF, chronic renal failure

Indian-Arab populations[2,11,14,33], the same argument was given by Moreira *et al*[15] for Brazilian sickle cell disease population. However, a study showed that even when transfusion was made from donors from the same racially oriented population, high levels of alloantibodies were still produced[34], and

this was explained by the high levels of Rh antigenic differences in ethnic African population.

In our study, majority of patients developed alloantibody with <10 units of red cell transfusion and some developed this complication even after one unit of transfusion. Early development of alloantibody in susceptible patient has also been described by others[35].

Certain alloantibodies may be difficult to detect; hence, techniques employed to detect such antibodies may be different and some evanescent antibodies may come and go; hence, the prevalence of the alloantibodies may not only be dependent on less or more sensitive techniques but also types of cell panel employed, zygosity of the particular antigen in the cell panel and time after transfusion when the testing was done to detect such antibodies.

It has been argued that centres which practice pre-storage leucodepletion or any type of leucocyte filtration may have less alloimmunization. The argument was found to be true for HLA alloimmunization; however, it has not been shown to be pertinent in development of antibodies against red cell antigens[36].

Alarif *et al*[37] showed that HLA-B35 might be relevant for alloimmunization in sickle cell disease. Others have pointed out the role of various HLA-DRB1 alleles in the alloimmunity to red cell antigens in sickle cell disease[38]. HLA antigen distribution was not studied in our patients will SCD who developed alloantibodies following red cell transfusion.

In our study SCD patient showed nine times more alloimmunization than those receiving more intense transfusions for thalassaemia major (11 vs. 1.2% for thalassaemia).

There are several reasons why sickle cell patients are alloimmunized more readily than other multitransfused patients. This has been extensively discussed by Yazdanbakhsh *et al*[3,39]. Very often sickle cell disease patients have ongoing inflammation which upregulates many of the genes in the immune system responding to danger signal associated molecular patterns released by ongoing tissue destruction and tissue necrosis as a result of sickle cell crisis. There is often racial mismatch between donors of the red cells and the recipients.

In Western countries, particularly in North European countries, where thalassaemia is rare, the prevalence of alloantibodies in thalassaemia patients is high, probably due to racial mismatch[36,40]. In India, studies in multitransfused patients with thalassaemia major have shown 1.5-8 per cent alloantibody formation (Table III). Only Jolly *et al*[17] showed a high prevalence (15.5%) of alloantibody in multitransfused thalassaemia major patients.

Most studies[39] on alloimmunization in SCD patients have shown that alloantibodies are formed against broad Rh locus antigens, *i.e*. e C e E D, Kell antigen and Duffy antigens. Hence, it has been suggested that extended phenotyping of blood involving all the Rh Kell and Duffy antigens may cut down this alloimmunization rate at least by 60-80 per cent. However, the time, finance and labour required to provide such a red cell unit may be worthwhile because of cost and time may increase several fold to find properly matched red cell units in a heavily alloimmunized patient. Moreover, such action also prevents the mortality and morbidity in these patients[41].

When the high throughput molecular typing of red cell antigens becomes available, it will be possible to provide improved matching of red cells for transfusion to sickle cell disease patient and prevent red cell alloimmunization to a large extent[41].

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***Conflicts of Interest*:** None.

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