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Original Research Article

Alloimmunisation in sickle cell patients of western Odisha: A tertiary care centre study

Chitta Ranjan Prasad[1], Susmita Behera[2], Yespal Sharma[3,*]

[1]*Dept. of Transfusion Medicine, Veer Surendra Sai Institute of Medical Sciences and Research, Burla, Odisha, India*
[2]*Dept. of Transfusion Medicine, MKCG Medical College and Hospital, Brahmapur, Odisha, India*
[3]*Dept. of Pathology, Veer Surendra Sai Institute of Medical Sciences and Research, Burla, Odisha, India*

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ABSTRACT

RBC carries numerous protein and carbohydrate antigens on their surface. Out of 347 red cell antigens recognized by international society of blood Transfusion, 308 antigens are clustered in 36 blood Group systems. Except naturally occurring anti-A and anti-B antibodies all others are unexpected. Out of these some like Duffy, Kell, Kidd, MNS, P and certain Rh types are considered clinically significant. Only few studies for prevalence of irregular red cell alloantibody have been done. Those studies were done either in general population or in thalassemia patients. Few studies were done on sickle cell disease patients but all are outside India and those are significant. But no studies have been done till now on prevalence of alloantibody in sickle cell disease patients in India. Again the western part of Odisha is with high patient load of sickle cell disease. This study is very useful for this part of Odisha as complication due to the alloantibody can be managed properly. Both the patients and the clinician will be benefited by this study.

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1. Introduction

Sickle cell disease is a hereditary haemoglobinopathy, characterised by chronic anaemia, recurrent painful episodes and irreversible organ damage. Transfusion of red cells is a common intervention to treat and prevent the complication. Patients with sickle cell disease have high risk of alloantibody formation. Alloantibody may cause haemolytic transfusion reaction (acute or delayed) or decrease in the survival of transfused RBCs.

Red blood cell alloimmunization results from the genetic red blood cell antigen disparity between donor and recipient or from mother and fetus. The first reports on alloimmunization date from the 17th century describing hydropic stillborns. This disease, today known as hemolytic disease of the fetus or newborn (HDFN), is caused by immune IgG antibodies from the mother directed against the red blood cells of the fetus

A red blood cell unit contain red cells that express an array of multiple alloantigens, each of which can potentially induce an antibody response. It is therefore surprising that humoral alloimmunisation to red cell is rare. Indeed, when ABO COMPATIBLE, D matched red blood cells are used, only approximately 3% of transfused patients become alloimmunized, even following multiple red blood cell transfusion.

The alloimmunisation frequency varies with both the blood group antigen and the underlying genetics and pathophysiology of the recipient. Alloimmunisation rate are substantially higher in sickle cell anemia.[1] the reasons for this are

1. Disparity of donor/recipient demography.

* *Corresponding author*.
E-mail address: yespal1983@gmail.com (Y. Sharma).

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2. Alteration in immunobiology due to sickle cell disease.
3. Lickage disequilibrium with immunoregulatory genes close to the globin gene.[2]

The red cell alloantibodies are not equally distributed among transfused patients. Rather patients who have made an alloantibody against one blood group antigen are more likely to make additional antibody often subsequent transfusion. Those not responding to antigen in initial transfusion are unlikely to develop the antibody. The two groups are responder and non-responder. These observations are practical ramification for management of patients requiring chronic transfusion therapy as sickle cell disease.

Matching blood for multiple antigens (e.g. kell, kidd &duffy) is both costly and time consuming. So many places matching for ABO & D is done during initial treatment and later on once the patient makes one red cell alloantibody, extensively matched blood is provided for subsequent transfusion, patient who does not make alloantibody continue to receive red blood cell matched only for ABO & D.

This saves the resources but results in development of at least one red cell alloantibody in responder, which would have been avoided.

1.1. Potential mechanisms

1. The recipient genetically negative for the antigens.
2. The transfused donor red cell carries the antigen.
3. The recipient MHC class-II molecules are capable of presenting a red cell allogenic peptide containing a variant amino acid found in the donor but not in the recipient.

1.2. Additional factors

1. Genetic determinants other than red cell antigen and MHC class-II.
2. Environmental factors affecting the donor limit.
3. Environmental factor s affecting the transfusion recipient.

1.3. Other genetic determinants

Rs660 polymorphism in the Ro52 gene is associated with kinetics of alloimmunisation in sickle cell disease patients,[2] although the function of Ro52 (also called SSA1 and TRIM21) is only practically characterised. It appears to be immunoregulatory gene products. Thus, a role for Ro52 in regulating alloimmunisation is logical; however correctly the association is only correlative and causal role is yet to be tested. The risk of alloimmunisation can be reduced by choosing blood matched for Rh and Kell groups in SCD.[3] Patients who are already alloimmunised should undergo extended red cell phenotypic matching (C, c, D, E, e, K, k, Jka, Jkb, Fya, Fyb, Kpa, Kpb, MNS, Lewis) with some centres also employing red cell genotyping to increase the accuracy of Rh typing, and in locating compatible units.

2. Materials and Methods

All the tests are done by gel card method. Liss/coombs card (Matrix), Card centrifuge (85g), Incubator (37^0C), Workstation, Pipettes (10, 25 & 50μl), Screening cell pane, Isotonic saline solution (LISS), Bottle top dispenser

Reagents: -The matrix AHG (Coombs) Test Card contains six microtubes, prefilled with a gel in a suitable buffer containing Anti-Human IgG and Monoclonal Anti-C_3d.

The matrix AHG (Coombs) Test Card is suitable for Direct Coombs test, Indirect Coombs test including compatibility testing, antibody screening and antibody identification.

2.1. Methods

The study was conducted in The Department of transfusion medicine and Department of Pathology VSSIMSAR, BURLA from November 2017 to August 2019 and the study was Prospective and observational study. The study was conducted on the Sickle cell disease patients coming for red cell transfusion to Blood bank, VSSIMSAR, Burla.

Principle:- As the Matrix gel card containing red blood cells is centrifuged under specific conditions, the red blood cells sensitized with antibody will agglutinate in presence of the Anti-Human Globulin reagent in the gel matrix and will be trapped in the gel column. The red blood cells, which do not get trapped in the gel matrix, are palleted at the bottom of the column. The reaction is then read and graded according to their reactivity pattern.

2.2. Inclusion criteria

1. Age 5-30 yrs.
2. Sickle cell patients with more than two transfusions**.**

2.3. Exclusion criteria

1. Patients with multiple transfusions due to any other haemoglobinopathy or any other medical or surgical causes.
2. Sickle cell patients with no history of transfusions**.**

3. Limitations

1. Small sample size.
2. Non availability of specific antibody identification facility.
3. High cost and short expiry of reagent.
4. Study included only patients coming to blood bank for transfusion of red cell.

4. Observation

Veer Surendra Sai Institute of medical science and research is a tertiary care institute situated at Burla in the state of Odisha. This institute has its own blood bank in the department of transfusion medicine. In view of high load of sickle cell disease patients a separate sickle cell unit is there with all high end tests for sickle cell patients.

1. Screening of total 110 patients was done in the department of transfusion medicine for alloantibodies.
2. All patients were confirmed for sickle cell disease by HPLC test done in our sickle cell unit.
3. Proper history of all the patients was collected in a pre-prepared format attached later.
4. All the history related to transfusion and transfusion related complications were collected carefully.
5. Three panel screening cell supplied by Tulip and matrix AHG gel card were used for the entire test.
6. Auto-control & DAT was done for all the patients.
7. Quality Control was done every day at the starting and end of the testing.

A total of 110 patients with sickle cell disease were included in the study after careful consideration of all the exclusion and inclusion criteria. Then all the patients were included in the study were screened for alloantibodies. All the observations were done visually and photograph of the gel-cards were kept for future reference. All the patients with screening test positive were sent to other higher centre where specific antibody detection facility was available. Those who were severely ill were transfused with extensively cross matched blood as life saving measure.

Demographic data of sickle cell disease patients who received regular blood transfusion:

1. Out of 110 patients 59 were male patients and 51 were female patients.
2. 53.63% are male of total patients.
3. 46.37% are female of total patients.
4. All the sickle cell disease patients as diagnosed by sickle cell Institute.
5. Distribution of patients as per age:
6. Out of 110 patients maximum no of patients are of age group 16yr-20yr i.e. 30 out of 110 patients.

It is 27.27% of total patients screened.

Distribution of patients among different blood groups:

1. Maximum numbers of patients are of O+ve blood group i.e. 44 out of 110.
2. It is around 40% of the total patients screened.

5. Results

Out of total 110 patients screened for alloantibody 15 patients were found to be positive for alloantibody. That is 13.64% of patients developed alloantibodies. Which is significant and requires immediate attention.

1. Among the 15 patients 7 were males and 8 were females. So the alloantibody distribution shows little female predominance.

Table 1: Association between alloantibody and gender

Gender	Present of alloantibody	Absent of alloantibody	%
Male	7	52	11.86%
Female	8	43	15.68%
Total	15	95	13.64%

6. Discussion

Till now there are no published data on incidence of alloimmunisation among sickle cell disease patients in western part of Odisha and India. Thus, study was aimed to investigate the frequency of alloimmunisation among these patients.

The rate of alloimmunisation observed in present study is 13.64% which is comparable to study done by L.A.M. Bashawri, Damman, Soudi Arbia,[4] who found it to be 13.7%. Study done by J Sin et al, amsterdom[5] and Wendell F. Rosse et al, Chicago[6] found it total 22% and 18.6% respectively, which is little higher than the present study. Another study done by Fekri Samarah et al, Palestine[7] found 7.76%, which is much lower than the present study. Except the last study all other study found higher frequency of alloantibody formation in sickle cell disease as mentioned in different literatures and books.

These differences in the rate of RBC alloimmunization among SCD patients support the importance of ethnic/genetic differences between patients and donors. Although the cost of antigen matching is high, further studies are needed to investigate the influence of this factor on the rate of alloimmunization. Another factor that could contribute to the relatively low rate in the last study is that SCD patients are not checked for RBC alloantibodies after each transfusion which may lead to missing the detection of transitory alloantibodies.[7]

Mean age of alloantibody production in present study is 22.2yrs. Which is 28.8yrs in study by L.A.M. Bashawri and 23.4yrs in study by J Sin et al. Study by Wendell F. Rosssr et al and F. Samarah also show similar result i.e. patients with older age (>20yrs) show highest rate of production of alloantibody.[8]

Two patients out of 15 patients in present study were of paediatric age groups. This is quite similar to most of the other studies. It is reported that SCD children who were first transfused at the age of 10 years and older had a higher rate of alloantibodies compared to those who were transfused before that age.[9]

Eight out of 15 patients are female in present study, showing slight female predominance. This is similar to the study by L.A.M. Bashawri and most of other studies. Only the study by F. Samarah found no difference in gender. It has been suggested in many literatures that the rate of alloimmunisation was greater for women than for men. The reason for this is more need of red cell transfusion and complications related to pregnancy.[10]

The predominant blood group in present study is O+ve followed by B+ve, A+ve and AB+ve. The study shows result similar to the study done by L.A.M. Bashawri and most of the other studies available.[11,12]

Comparison of different studies with present study

Table 2: Comparison of different studies with present study

Study	Total No of patients	No of patients positive	% of positive patients
L.A.M. Bashawri	350	48	13.7%
J Sins et al	250	54	22%
Wendell F. Rosse et al	200	36	18.6%
Fekri Samarah et al	116	9	7.76 %
Present study	110	15	13.64%

7. Conclusion

Clinically red cell alloantibody is associated with:-

1. Hemolytic dis of fetus & new born(HDFN
2. Hemolytic transfusion reaction
3. Decrease in survival of transfused red cells
4. Some cause destruction of incompatible red cells within hours, minutes to days

It is found in this study that in the sickle cell disease patients, the prevalence of alloantibodies is higher than in the general population and is associated with many complications.

As sickle cell disease patients require multiple transfusions in their lifetime they should always be screened for alloantibody. The red cell transfused to them should be screened so that development of alloantibody can be avoided.

As this part of Odisha has high incidence of sickle cell disease and many people died due to complications of this disease, this study is an eye opener. Screening of alloantibody should be made mandatory for these patients and for the donor‘s blood. Moreover, while transfusing red blood cells to these patients, leukofiltration should be used.

8. Conflict of Interest

The authors declare that there are no conflicts of interest in this paper.

9. Source of Funding

None.

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Author biography

Chitta Ranjan Prasad, Associate Professor

Susmita Behera, Assistant Professor

Yespal Sharma, Senior Resident

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