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Transfusion Medicine

RED CELL ALLOIMMUNIZATION IN MULTI TRANSFUSED ONCOLOGY PATIENTS IN A TERTIARY CARE HOSPITAL

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ABSTRACT **Introduction:** Blood transfusion is an integral part of multifaceted therapy in oncology patients owing to the intense marrow suppression resulting from chemotherapy, radiotherapy, or disease pathology. Transfusion dependence exposes these patients to consequences of blood transfusion including alloimmunization against one or more red cell antigens. Alloimmunization can result in delayed hemolytic transfusion reactions on subsequent transfusion of antigen- positive donor RBCs. **Objectives:** To assess the factors and their association with the development of antibodies in multiple transfused individuals. **Materials & Methods:** A hospital-based Descriptive Study was conducted among 100 multi-transfused oncology patients. All oncology patients aged above 18 years who had received ≥ 2 packed red blood cell transfusions were included, and post-hematopoietic stem cell transplant patients were excluded. After obtaining informed consent, blood grouping, Rh typing and antibody screening were performed on all blood samples. Antibody identification of screening positive samples was done using a commercial 11-cell panel of reagent red cells (BioradID Dia-panel). The statistical analysis was done using SPSS version 22.0 software. **Results:** In the study population, only 1% of multi-transfused oncology patients developed alloimmunization. The association of alloimmunization with the total number of transfusions (p value = 0.017) and, the cumulative number of PRC and PC transfusions (p value = 0.045) is statistically significant in this study. The mode of cancer treatment undergone by the patient also has a significant association with the total number of transfusions received by the patient. **Conclusion:** The rate of alloimmunization is low (1%) in multi-transfused oncology patients. Routine pretransfusion antibody screening before crossmatching on patient blood samples should be mandated as part of pretransfusion testing in multi-transfused patients to ensure transfusion safety.

KEYWORDS : red cell alloimmunization, multi transfused, oncology

INTRODUCTION

Over 85 million units of packed RBC are transfused globally.(Iqbal et al., 2017) The transfusion of serological safe blood is essential in patient blood management in blood transfusion services. The discovery of the ABO blood group system by Karl Landsteiner in 1900 and the development of the Anti-globulin Test by Coombs, Mourant, and Race in 1945 led to the marked reduction in fatalities associated with blood transfusion and identification of various alloantibodies. (Rajeev T et al., 2021) Transfusion safety cannot be achieved solely through comprehensive testing for infectious markers; it also requires protection against haemolytic transfusion reactions brought on by alloimmunization against red cell antigens. (Makroo et al., 2014)

Alloimmunization is the development of antibodies to cell surface proteins (antigens) from a different member of the same species. (Castleman & Kilby, 2020) As blood is routinely matched with respect to major blood group antigens i.e., ABO and Rh D antigen, there is a high probability that the donor will have minor blood group antigens not present in the recipient which will result in alloimmunization. (Bilwani et al., n.d.)The antigenic difference between donor and recipient, the patient's immune status and the immunogenicity of the RBC antigen are some of the factors that influence the formation of alloantibodies. (Valle Neto et al., 2018)

Repeated blood transfusions can produce alloantibodies against one or more red cell (RBC) antigens, which complicate subsequent transfusions. Alloantibodies can interfere in the crossmatch testing and therefore can cause delays in obtaining compatible blood and are also sometimes associated with the delayed type of hemolytic transfusion reaction. (Bhuva & Vachhani, 2017) Red blood cell (RBC) alloimmunization, or the formation of antibodies against non–self-antigens on RBCs, may occur after exposure through transfusion or pregnancy. These antibodies may be clinically significant in both settings, leading to delayed hemolytic or serologic transfusion reactions or hemolytic disease of the fetus and newborn (HDFN). (Hendrickson & Tormey, 2016) The concomitant presence of autoantibodies may further complicate these hazards. (El-Beshlawy et al., 2020)

The risk of alloimmunization is high in patients receiving multiple transfusions such as patients having thalassemia major, aplastic anaemia, sickle cell disease, hematologic malignancies, chronic renal failure, and cancer patients receiving chemotherapy. The most important determination for any transfusion is to exclude the presence of clinically significant alloantibodies in the patient's blood before selecting RBC for transfusion. (Mangwana et al., 2019)

Objectives

To assess the factors and their association with the development of antibodies in multiple transfused individuals.

MATERIALS & METHODS

This was a hospital-based Descriptive Study conducted among multi-transfused oncology patients. The Study protocol was approved by the institutional review board and the Human Ethics Committee. The study was conducted in accordance with the principles of good clinical practice. Sampling was done using consecutive sampling All oncology patients (male and female) aged above 18 years who had received ≥ 2 packed red blood cell transfusions were included. Patients who have undergone Hematopoietic stem cell transplantation and who were not willing to give consent were excluded from the study.

After taking written informed consent, data collection was done using a proforma filled in by the investigator. Blood samples of study subjects received were used for the study (2ml of plain blood sample and 2ml of EDTA anti-coagulated blood sample). Blood grouping, Rh typing and antibody screening were performed on all blood samples. Antibody screening was done using commercial 3-cell panel red cells (Biorad Id-Diacell I-II-III) and polyspecific antihuman globulin (anti-IgG + c3d) incorporated gel cards. Samples with positive antibody screens were subjected to antibody identification using a commercial eleven-cell panel of reagent red cells (Biorad ID Dia-panel) and polyspecific antihuman globulin (anti-IgG + C3d) incorporated gel cards. The antibody screen and identification test were performed as per the manufacturer's instructions given in the package insert.

The data was entered into Microsoft Excel software and statistical analysis was done using SPSS version 22.0 software

OBSERVATION AND RESULTS

The present study is a hospital-based Descriptive Study conducted among 100 multi- transfused oncology patients in a tertiary care hospital. The observations of the present study are mentioned under various headings below.

Table No 1: Distribution Of Study Subjects According To Age, Gender & Blood Group (n =100)

Age group (years)	Frequency (N)	Percentage (%)
31-40	4	4%
41-50	8	8%
51-60	31	31%

Above 60	57	57%
Total	100	100%
Gender of study subjects		
Male	52	52%
Female	48	48%
Total	100	100%
Blood group		
A POSITIVE	22	22%
B POSITIVE	32	32%
O POSITIVE	22	22%
AB POSITIVE	12	12%
A NEGATIVE	3	3%
B NEGATIVE	3	3%
O NEGATIVE	5	5%
AB NEGATIVE	1	1%
Total	100	100%

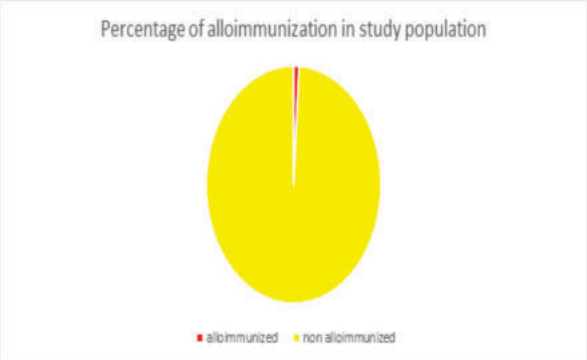

Figure No 1: Percentage Of Alloimmunization In Study Population

Among the 100 patients studied, only 1% developed alloimmunization to red cell antigens.

Table No:2 Association Between Type Of Malignancy And Number Of Transfusions Analysed Using The Chi-square Test (n=100)

Type of malignancy	Total number of transfusions					P value
	<= 5	6-10	11-15	16-20	>20	
Haematological malignancy	12	5	1	0	1	0.965
Non-haematological malignancy	52	19	6	1	3	

The Association between Haematological malignancy and non-haematological malignancy with the number of transfusions is not statistically significant (p=0.965).

Table No: 3 Association Between Mode Of Treatment And Number Of Transfusions Analyzed Using The Chi-square Test (n=100)

Mode of	Total number of transfusions					p value
treatment	<= 5	6-10	11-15	16-20	>20	
Chemotherapy	31	9	3	0	1	0.099
Radiotherapy	1	2	0	0	0	0.000*
surgery	3	3	0	0	1	0.030*
Chemotherapy+ Radiotherapy	11	3	4	0	0	0.080
Radiotherapy+ surgery	4	1	0	1	1	0.003*
Chemotherapy+ surgery	10	3	0	0	1	0.018*
Chemotherapy+ Radiotherapy+ surgery	4	3	0	0	0	0.003*
Values are analysed by using the chi-square test. (*) represents a statistically significant difference.						

The association between modes of treatment including Radiotherapy alone, Surgery alone, combined Radiotherapy and surgery, combined Chemotherapy and surgery, combined Chemotherapy, Radiotherapy, and surgery with the number of transfusions are statistically significant.

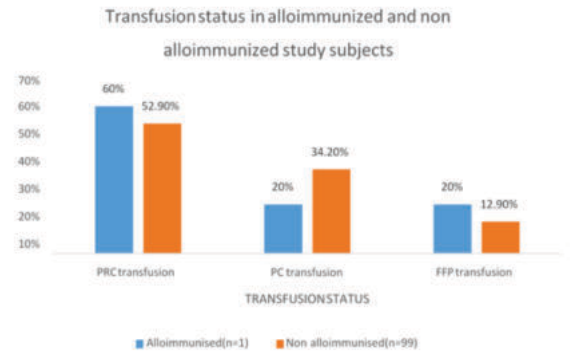

Figure No 2 Transfusion Status In Alloimmunized And Non-alloimmunized Study Subjects (n=100)

The percentage of PRC transfusions in the alloimmunized study population is higher than in the non-alloimmunized group of patients.

Table No:4 Basic Features Of Alloimmunized And Non-alloimmunized Multi- Transfused Oncology Patients By Independent T-test (n=100)

	Alloimmunized (1) (mean ± S.D.)	Non alloimmunized (99) (mean ± S.D.)	p value
Age (years)	70 ±0.00	61.2 ± 9.63	0.365
Total No. of transfusion	20 ± 0.00	5.75 ± 5.83	0.017*
Total number of PRC and PC transfusions	16.00± 0.00	50.4 ± 5.55	0.045*
Total number of PRC transfusions	4.00 ± 0.00	3.12 ± 1.42	0.537
Total number of PC transfusions	12.00 ± 0.00	4.87 ± 7.25	0.339
Values are analysed by using the independent t test. (*) represents a statistically significant difference.			

The association between alloimmunized and non- alloimmunized study subjects with the total number of transfusions is statistically significant (p value = 0.017).

The association between alloimmunized and non-alloimmunized study subjects with the total number of PRC and PC transfusions is statistically significant (p value = 0.045).

DISCUSSION

Oncology patients frequently require chronic transfusion support as they develop cytopenia due to intense marrow suppression resulting from chemotherapy or radiotherapy or the disease process itself and during surgical interventions. Owing to transfusion dependence these patients are at increased risk for complications of blood transfusion including alloimmunization to one or more red cell antigens. The proposed risk for red cell alloimmunization in multi-transfused patients is applicable to oncology patients despite the immuno-suppressed status of the study population. Subsequent transfusion therapy becomes challenging in patients with alloantibodies due to delays in pretransfusion testing and difficulty in finding the adequate number of antigen- negative crossmatch compatible red cell unit due to the risk of delayed hemolytic transfusion reaction.

In this hospital-based Descriptive study, multi-transfused oncology patients who received two or more PRC transfusions attending the transfusion medicine department were enrolled as per the steps mentioned in the methodology. Pretransfusion antibody screening was performed on all patients and screening-positive samples were subjected to antibody identification to look for the presence of RBC alloantibodies. This study was an effort to detect the proportion of alloimmunization, specificity of alloantibodies against red cell antigens, the factors influencing their development and to determine the effect of treatment modalities in transfusion requirement among the pertained study population.

The total number of subjects enrolled in the study was 100 multi-transfused oncology patients who received two or more PRC transfusions in the study period. The mean age of the study population

is 61.28 ± 9.61 years. The lowest age was 33 years and the highest was 83 years with 57% of the population having an age >60 years. 52% of patients were males and 48% were females.

Mohsin et al in a study of 150 oncology patients reported that the mean age of study population was 42.90±12.10 years and the male-to-female ratio was 44:106. (Mohsin, 2013)

The most common blood group in the study population was B positive in 32% of patients and the least common was AB negative in 1%. The distribution of A, B, O and AB blood groups are 25%, 35%, 27% and 13% respectively whereas 88% are Rh D positive and 12% are Rh D negative in the study population. Patidar et al in a systematic review of the distribution of ABO & Rh (D) blood groups in India found that the overall distribution of the A, B, O and AB blood groups is 23.16%, 34.10%, 34.56% and 8.18%, respectively. 94·13% are Rh(D)-positive and 5·87% are Rh(D)- negative in India whereas in Kerala it is 90.88 and 9.12% respectively. The distribution of the ABO blood group in Kerala is 26.33% A, 28.99% B, 37.84 % O and 6.84% AB blood groups respectively. (Patidar & Dhiman, 2021)

The study population was initially classified into Haematological and Non-Hememato logical (solid organ) malignancies contributing to 19% and 81% respectively. The mean age of patients with Haematological malignancies was 61.18±10.17 years and non-Haematological malignancies was 61.68±7.34 years. The male-to-female ratio is 8:11 in haematological and 44:37 in solid organ malignancies respectively.

In a study, 16% of patients had haematological malignancies with a mean age of 44.17 ± 15.74 years and 84% of patients had non-Haematological malignancies with a mean age of 42.67± 11.35 years respectively. The male-to-female ratio in haematological malignancies was 18:6 whereas 28:98 in solid organ malignancies. (Mohsin, 2013)

The Haematological malignancies found in the study population were multiple myeloma, AML, NHL, Hodgkins lymphoma, and CLL with 57.89%, 15.78%, 15.78%, 5.26%, 5.26% and 5.26% distribution respectively.

In terms of the total number of haematological malignancies, acute lymphocytic leukaemia, myelodysplastic syndromes, and acute myeloid leukaemia accounted for 26.5%, 19.3%, and 15.7%, respectively in a study. (El Fetouh et al., 2020)

Mohsin et al reported that among haematological malignancies the most common was NHL (45.9%) and ALL (20.9%). The mean number of transfusions was the highest in ALL (14 in number). (Mohsin, 2013)

In patients with solid organ malignancies, the most common were carcinoma breast and carcinoma rectum contributing to 12.34% each, carcinoma lung in 11.11%, and Carcinoma bladder, carcinoma ovary and carcinoma pharynx comprising 8.64% each. 7.4% of patients had carcinoma colon.

Due to its immunosuppressive effects, chemotherapy may decrease the chance of alloimmunization regardless of the presence of cancer or the number of red blood cells transfused in the patients. (Solh et al., 2016)

The most common modality of treatment used was chemotherapy in 82%, radiotherapy in 35% and surgery in 35% of patients in different combinations. Chemotherapy alone was used in 44%, chemoradiation in 18%, and a combination of chemotherapy and surgery in 14% of patients as therapy.

On analyzing the ratio of the total number of transfusions given to patients undergoing different treatment modalities, the highest was found among patients undergoing combined radiation and surgery with a ratio of 9 followed by surgery alone with a ratio of 7.28 and radiotherapy alone with a ratio of 6.3 in this study. The highest ratio of total No. of transfusion in patients with Haematological malignancies was found in NHL and non-haematological malignancies were found in Sarcoma left maxilla respectively.

When blood component transfusion in haematological malignancies in the present study is analyzed the highest ratio of PRC transfusion was seen in NHL followed by CLL and AML. In the case of PC transfusion, the highest ratio was found in NHL followed by Multiple myeloma. In AML patients 70% were PRC transfusions and 30% were PC transfusions. In Multiple myeloma patients, PRC and PC transfusions contributed 50% each.

The mean number of PRC units transfused was 4.21 among hemato-oncologic patients. (Mohd Noor et al., 2019) The mean number of transfusions in haematological malignancies was 10.79 ± 6.0. (Mohsin, 2013)

In solid organ malignancies, the analysis of blood component transfusion revealed that the highest PRC transfusion ratio of 6 and PC transfusion ratio of 30 was found in a case of sarcoma left maxilla. In this patient, 83% of transfusions were PC units. In Ca breast 60% were PRC and 40% were PC transfusions. In Ca bladder 45.4% were PRC, 36.3% were PC and 18.2% were FFP transfusions.

In this study, 100 patients received a total of 610 units of blood transfusions, of which 324 units were PRCs. 1% of patients developed alloimmunization. The mean age of the alloimmunized population was 70 ± 0.00 years.In the study population, 1.9% of the males were alloimmunized whereas none of the female patients was alloimmunized. The association between gender and alloimmunization was not found to be statistically significant in the current study.

The red cell alloimmunization in multi-transfused oncology patients was 0.30%. Here 94.5% of alloimmunized patients were females and 5.5% were males. (Mangwana et al., 2019)

CONCLUSION

The rate of alloimmunization is low (1%) in multi-transfused oncology patients. There is a significant association between the total number of transfusions received with alloimmunization to red cell antigens. The mode of cancer treatment undergone has a significant association with the total number of transfusions received by the patient. Routine pretransfusion antibody screening before crossmatching on patient blood samples should be mandated as part of pretransfusion testing in multi-transfused patients to ensure transfusion safety. The patients with identified alloantibodies can be given antigen-negative units for that antigen to which the patient developed alloimmunization to minimize antibody-mediated destruction of transfused RBCs. Provision for phenotype-matched blood products may further decrease the rate of alloimmunization in this patient population.

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