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Anti-Erythrocyte Alloimmunisation in the RH System during Chronic Kidney Disease: Frequency in Patients at the Yaoundé I University Teaching Hospital

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Abstract

Background: Blood transfusion is a medical procedure that consists in administering total blood or blood products to requiring patients. In case of transfusion incompatibility, de-immunization occurs in the recipient. **Objectives:** The aim of this investigation was to determine the post-transfusion frequency of anti-erythrocyte alloimmunisation developed in patients with terminal renal disease. **Methods:** For this purpose, a cross-sectional descriptive study was conducted for two months at the Yaoundé I University Teaching Hospital. The participants were patients enrolled at the Department of Nephrology and Hemodialysis of this health facility. Alloantibodies were detected and identified by the direct Coombs and red blood cell tests. Data analysis was conducted with tools from the statistical software R-version 4.1.1. **Results:** Forty-six patients with terminal renal disease were enrolled out of which 41% were women and 59% were men with the overall prevalence of anti-erythrocyte alloimmunisations (anti-rhesus alloimmunisations), at 47.82%. The frequencies of antigens from the Rh system were 89.13%, 67.39%, 78.26%, 32.61% and 30.43% for "D", "E", "e", "C", and "c" antigens, respectively. Further findings revealed the "O" group as the most common blood group (43.47%) while the rates of alloantibodies were 60% for IgG, 32% for IgM and 8% for IgA. **Conclusion:** According to these foundings and aiming at reducing anti-erythrocyte alloimmunisation, it appears crucial to limit blood transfusions to their strict indications and to ensure that extended

phenotyping is conducted prior to isogroup blood transfusions, otherwise, the best indicated.

Subject Areas

Hematology

Keywords

Terminal Renal Disease, Alloimmunisation, Alloantibodies

1. Introduction

Blood transfusion refers to a medical procedure that consists in administering total blood or specific components of the blood to needy individuals [1]. This procedure was initiated in the 20th century (in 1901, more precisely) with the discovery of the ABO blood groups by Karl Landsteiner [2]. Nowadays, blood transfusion stands out as a peculiar branch in medicine, at the junction of almost all the specialties in the medical field. Despite tremendous research works over the last 50 years; it is not yet possible to produce substitutes that are identical to the labile blood products used today; explaining the tediousness of the theme supporting the present investigation [3]. Since it can be dangerous although very effective as a therapy, it is only used as the latest option.

One of the major immunohematological risks of transfusional therapy in polytransfused patients is anti-erythrocyte alloimmunisation, which can cause serious hemolytic accidents and lead to cases of transfusional impasses [4]. In Cameroon as in many African countries, blood transfusion is essentially performed based on the ABO and Rh-D compatibility. Otherwise, investigation through compatibility in other erythrocyte systems such as Rh, Kell, Kidd, Duffy, Lewis and MNSs for which antigens are equally immunogenic are rarely performed. Such a practice is source of risks of alloimmunisation, which can lead to serious clinical complications in polytransfused individuals likely, for instance, to compromise the obstetrical future of female individuals [5]. More specifically, kidney disease is known to associate with progressive loss of renal functions affecting erythropoiesis. In terminal renal disease, the patient is therefore, subjected to a high frequency of red blood cell transfusion then, with a higher risk of alloimmunisation. Out of 81 in an investigation conducted in India, 9.8% of patients who received multiple transfusions in connection with chronic kidney disease developed red cell alloantibodies [6]. In 2017, a study conducted in France revealed an alloimmunisation rate of 10.43% in patients with chronic kidney disease [7]. In Côte d'Ivoire, the overall prevalence of anti-erythrocyte alloimmunisation in a similar population was 14.2% [8].

Anti-erythrocyte alloimmunisation is regarded as aserious public health issue, source of post-transfusion accidents and therapeutic failures, especially in coun-

tries with limited resources. This piece of work is a contribution to the overall struggle at improving the immuno-hematological blood transfusion safety and preventing alloimmunisation in patients with terminal renal disease.

2. Methods

2.1. Study Type and Population

This cross-sectional study was conducted over a period of 2 months (July 22nd through September 19th, 2021) in the Department of Nephrology and Hemodialysis of the Yaounde I UTH, a health unit with 40 beds. The target population consisted of patients with terminal renal disease of all ages admitted in the department of nephrology. Consecutive sampling was accordingly conducted and, patients who consented were enrolled.

2.2. Selection Criteria

Sampling was consecutive. Patients defined as having end-stage renal disease and polytransfused, regularly followed at the Hemodyalysis Department of the University Hospital of Yaoundé (CHUY) were included; Monotransfused patients followed outside the CHUY were not included.

2.3. Sampling and Biological Analyses

Three milliliters of venous blood were collected in a dry test tube containing ethylene diamine tetra acetic acid. All specimens were thereafter conveyed without delay to the Immunohematology laboratory for analysis.

2.4. Blood Grouping in the ABO System

The ABO blood grouping was performed according to Beth Vincent and Simonin protocoles. Determination of Rhesus antigen "D" was achieved with monoclonal antibodies supplied by Cypress® and a rhesuscope.

2.5. Semi-Extended Phenotyping in the RH System

Semi-extensive phenotyping consisted in testing patients' red blood cells for Rh-system antigens other than D, C, c, E and e. The antibodies test indicators used were provided by Cypress Diagnostics®.

2.6. Testing Irregular Agglutinins

The test for irregular agglutinin was used to identify the antibodies that are responsible for alloimmunisations. Detection of irregular antibodies was performed by direct Coombs' with polyvalent Coombs reagent provided by Cypress Diagnostic®. Antibodies identification in Coombs-positive patients was performed with the "ionic strength solution" (LISS-Coombs) that identified the type of the immunoglobulin or C3D fraction of complement, alongside with an ID-DiaPanel red cell panel.

2.7. Data Processing and Statistical Analysis

The collected data were recorded with Microsoft Excel software 2016 and the statistical analysis of the data was performed with the R version 4.1.1 statistical tool. The variables studied were sex, age, the average of packed units of *red cells* transfused, frequency of transfusions, ABO and HR phenotype; frequency of alloimmunisations and the type of antibodies identified. Qualitative variables were presented as frequencies while quantitative ones were presented in terms of means ± standard deviation. A comparison of proportions was done with the Chi^2 test when the expected number of patients was greater than 5, and Fisher's test was otherwise. The Student test was used to compare the means of the different groups in the study population. All these tests were carried out at $\alpha = 5\%$ threshold.

3. Results

3.1. Distribution of the Study Population According to Socio-Demographic Characteristics and Clinical History

Overall, 46 patients were enrolled. The table below gives the distribution of the study population according to socio-demographic characteristics and clinical history:

From Table 1, the study included 19 women (41%) and 27 men (59%) for a sex ratio of 1.42; with an average age of 47.73 ± 16.29 years. The average number of transfused units was 2.87 ± 1.13; while the average frequency of blood transfusions per month was estimated at 2.37 ± 1.31 (2.74 ± 1.43 in men and 1.84 ± 0.90 in women).

3.2. Distribution of the Population According to Immunohematological Data

- **Distribution according to "ABO" and Rh D antigens**

Table 2 displays the frequency of ABO and Rh D blood groups in the study population according to sex.

It reveals that the overwhelming characteristics were D positive (≈90%) and A group that was almost four times as frequent as B group.

Table 1. Socio-demographic characteristics and clinical history of the population.

Parameters	Men M ± Et	Women M ± Et	Total M ± Et
Years (M ± SD)	47.93 ± 15.93	47.42 ± 17.23	47.73 ± 16.29
Mean of transfused units/per month (per year or per transfusion)	2.89 ± 1.15	2.84 ± 1.12	2.87 ± 1.13
Mean of frequency de transfusion/Month	2.74 ± 1.43	1.84 ± 0.90	2.37 ± 1.31

M ± SD = Mean ± Standard Deviation.

Table 2. Sex distribution of ABO and Rh-D blood groups at the UTH of Yaounde I between July and September 2021.

Rh D / GS ABO	D (positive) n (%)	D (negative) n (%)	Total n (%)
A	10 (21.73)	0	10 (21.73)
AB	8 (17.40)	1 (2.17)	9 (19.58)
B	5 (10.87)	2 (4.34)	7 (15.21)
O	18 (39.13)	2 (4.34)	20 (43.47)
Total	**41 (89.13)**	**5 (10.87)**	**46 (100)**

Table 3. Distribution of Rh system antigens (D, C, c, E, e) according to sex.

Antigen RH	Men n (%)	Women n (%)	Total n (%)
D	25 (54.35)	16 (34.78)	41 (89.13)
C	7 (15.22)	8 (17.39)	15 (32.61)
c	19 (70.37)	12 (30.43)	31 (67.39)
E	22 (47.82)	14 (30.43)	36 (78.26)
e	8 (17.39)	6 (13.04)	14 (30.43)

Table 4. Distribution of alloantibodies developed in chronic renal disease patients.

Antibodies	Men n (%)	Women n (%)	Total n (%)
Ig A	1 (4.54)	1 (4.54)	2 (9.09)
Ig G	9 (40.91)	4 (18.18)	13 (59.09)
Ig M	4 (18.18)	3 (13.64)	7 (31.82)
Total	14 (63.64)	8 (36.36)	22 (100)

- **Semi-extended phenotyping**

Investigation through the semi-extended phenotyping revealed sets of data that were summarized as displayed in Table 3 for the Rh system antigens.

Overall, the D and E overwhelmed the rates of detection in both males and females, with a relative higher frequency in male.

3.3. Prevalence of Erythrocyte Alloimmunisation and Alloantibodies

Alloimmunisation in the present survey affected 22 patients with a frequency of 47.8%. Out of the 22 patients affected, 8 (17.39%) were male and 14 (30.43%) were female.

- **Frequency of alloantibodies during alloimmunisations**

Likewise, Table 4 compiles pieces of data collected on alloantibodies accord-

ing to the sex of participants:

According to the table above, IgG was the most frequent immunoglobulin (60%), followed by IgM (32%); which immunoglobulins are characteristic of immunizations in CKD patients.

4. Discussion

Anti-erythrocyte alloimmunisation is the body response expressed subsequent to administration of foreign erythrocyte antigens (which are not present on the surface of the recipient's red blood cells) [9]. It is a major immunological risk in patients whose survival depends on multiple blood transfusions. The objective of the present study was to determine the frequency of anti-erythrocyte alloimmunisation in patients with terminal renal disease at the Yaoundé I University Teaching Hospital.

The frequency of anti-erythrocyte alloimmunisation recorded in patients with kidney failure was 47.82%. This high rate reflects the high frequency of blood transfusions in chronic renal disease patients and can also be justified by the limitation in the pre-transfusion immuno-hematological screening tests panel at the Yaoundé I UTH. In fact, the absence of systematic extensive phenotyping prevents the total identification of donor antigens in the least immunogenic systems, favouring thereby, incompatibilities in the recipient. This frequency is higher compared to the one reported by Habibi *et al*. [10] in a study conducted in Paris (France) on 405 patients with chronic kidney disease (1.72%). It is also higher compared to the rate observed by Frigoo *et al*. [7] in another investigation conducted on 31 hemodialysis patients (10.43%). This could be justified, at least partially, by financial resources limitations in the current general context, in connection with technical and human resources that are known to highly impact investigations in many developing countries around the globe. Further, the findings from the present survey are similar to those reported by Ngo Sack *et al*. [11] in a previous investigation through antierythrocyte alloimmunisation on 110 polytransfused and hemodyalised patients in Cameroon (46.36%). Likewise in 2018, Ifeoma Obi *et al*. [11] reported a prevalence rate of 33.2% of antierythrocyte alloimmunisation in a study conducted in Nigeria. This similarity associated with invariably high rates is typically consistent with various aspects related to human and financial resources in developing countries discussed above. The study population was 46 (59% of male and 41% of female, sex ratio: 1.42). This higher frequency of male is consistent with general epidemiological findings suggesting that women are more likely to be protected from chronic kidney disease. Otherwise, they are less likely to experience the terminal stage of chronic renal disease. Several hypotheses have been pointed out to afford explanation to this women's protection. One such is a renoprotective effect of oestrogens, while the other suggests the favourable hemodynamic and/or structural renal architecture [12]. Both hypotheses could combine to justify the resistance observed in female. This higher frequency observed in male is also similar to those observed

in Malaysia (Shafini Mohamed *et al.,* 2018) [13], 55.8%; in line with the above hypotheses on female protection.

Data analysis also revealed that the "O-group" associated with Rh-positive predominated (39.13%). This is likely due to the antigenic diversity within the study population; while the O-group is known to be most common in general. Findings from Malaysia (Shahini Mohamed *et al*., 2018) [13] and Cotonou-Benin (Tatia Baglo *et al*., 2017) [14] are consistent with the predominance of O-Rh+-group. The related frequencies recorded in both investigations were 37.3% and 49.9%, respectively.

Alloantibody testing in the present investigation was performed after the semi-phenotyping for Rhesus system antigens (D, C, c, E, and e). Blood grouping in this system revealed the following frequencies: 89.13% D, 32.61% C, 67.39% c, 78.26% E and 30.43%; overall 89.13% of Rhesus-positive individuals and 10.87% of Rhesus-negative with a predominance of D antigens, followed by E and c antigens for further details. The target alloantibodies tested by the direct Coombs test revealed alloimmunisation rate of 47.82%. The detected alloantibodies underwent further identification for more specificity. Related findings indicated IgG (59.09%) and IgM (31.82%). This could be explained by the fact that IgG (warm antibody detectable at 37˚C - 40˚C) is the main antibody detected during erythrocyte alloimmunization. The major cause of hemolysis is followed by IgM (optimum temperature of 4˚C). This observation was also made in 2017 by Achargui *et al*. [15] in a survey conducted in a polytransfused population of renal failure patients. These authors also observed higher rates of warm and cold alloantibodies with a similar proportion trend (30% IgG and 18.03% IgM, respectively).

These results suggest the importance of systematic screening for extensive erythrocyte phenotyping before any blood transfusion in order to mitigate or prevent incompatibilities events, the risk of rejection and therapeutic failure.

Limitation of the Study

The purpose of this study is to explore post-transfusion frequency of antiérythrocyte alloimmunisations developed in patients with a terminal renal disease. A longitudinal study on a larger population should be done to better elucidate the long-term consequences in chronic kidney patients who should undergo incompatible blood transfusions in the least immunogenic blood group systems.

5. Conclusion

The overall frequency of alloimmunisation amongst patients with terminal renal disease at the Yaoundé I Teaching Hospital was 47.82%. O-group predominated (43.47%) while the rates of antigens within the Rhesus system were 89.13% "D", 67.39% "E", 78.26% "e", 32.61% "C" and 30.43% "c". Identified alloantibodies were IgG (60%) and IgM (32%). It comes with the necessity to implement preventive strategies through EBCs phenotyped transfusion to patients with the

least immunogenic systems (including Rh, Kell, Duffy); and to carry out a systematic search for irregular agglutinins in all patients prior to any blood transfusion for optimal transfusion safety.

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Contributions of the Authors

Kévine Nelly Dedjo carried out the collection of biological data, its interpretation and the writing of the manuscript. Romaric De Manfouo Tuono and Peguy Martial Mbianda Tchuessi, supervised the experimental phase, interpreted the data and made a major contribution to the writing and revision of this piece of work, just as Maryline Seuko Njopwouo, Foutse Yimta and Pierre René Fotsing Kwetche. Josué Simo Louokdom contributed in the interpretation of data, the statistical analysis and the writing of the manuscript.

Patient Consent for Publication

Written informed consent was obtained from parents/guardians, and assent by the minor were obtained.

Ethical Considerations

This study was approved by the Committee of the Institutional Ethics and Research of the Université des montagnes (Reference N˚ 2021/120/UdM/PR/CIE). Authorisation for data collection and analysis of samples from eligible patients was obtained from the UTH of Yaounde I (Refernce N˚ 4582/AR/CHUY/DG/DGA/CM/PRC). Before starting the study, an informative letter on the objectives of the study, its benefits and risks were given to the participants. For eligible participants, we obtained their free informed consent with signature on the form. Confidentiality of the research results was respected by using a unique code for each patient.

Data Availability

The data used during our study for the write-up of this article are carefully kept by the corresponding author.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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