International Journal of General Medicine

Dovepress

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ORIGINAL RESEARCH

Red Cell Alloimmunisation Among Sickle Cell Disease and Thalassemia Patients Following Rh- and K-Matched Red Cell Transfusion in Southwestern Saudi Arabia: A Multicenter Study

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Background: Alloimmunisation remains a major consequence of blood transfusion among sickle cell disease (SCD) and thalassemia patients due to the exposure to non-self-red blood cell (RBC) antigen. The complication is associated with transfusion reactions and delayed transfusion procedure because of the difficulty of finding compatible blood. This study aims to determine the prevalence of alloimmunisation to RBC and alloantibody specificities among SCD and thalassemia patients in, an endemic area of SCD and thalassemia, Jazan province of Saudi Arabia, from three major hospitals.

Methods: This is a retrospective, multicenter cross-sectional study conducted on 1027 patients with SCD and thalassemia, which received Rh/K matched transfusions in 2019 in the three centers. Demographic data and medical records of participants from three transfusion institutions were collected and analysed.

Results: A total of 1027 were enrolled in the cohort; 906 (88.2%) and 121 (11.8%) patients with SCD and thalassemia, respectively. There were 483 (47%) males and 544 (53%) females with median age of 15 (range 1–48). Among the studied population, 78 were alloimmunised with an overall alloimmunisation rate of 7.6%. These patients developed a total of 108 alloantibodies, and anti-E was the most detected antibody (25.9%) followed by anti-K (24.1%).

Conclusion: The overall rate of alloimmunisation to RBC antigen among the studied population in Jazan was low compared to other areas in the country. Most alloantibodies detected were against E and K antigens. The knowledge of most encountered alloantibodies in our population will aid in selecting the most appropriate antigen-negative red cells. Further research, however, is needed to explore factors associated with residual risk of alloimmunisation in these patients.

Keywords: sickle cell disease, thalassemia, red cell transfusion, alloimmunisation, alloantibodies

Introduction

Sickle cell disease (SCD) and thalassemia are the most widespread monogenic hemoglobinopathies worldwide and remain global health burdens.[1] The prevalence of the two disorders in Saudi Arabia varies significantly between geographical regions.[2–4] The pathophysiological effect in both disorders results in red blood cell (RBC) destruction and anemia, which result in patients requiring blood-transfusion therapy frequently. Blood transfusion is often the only effective, lifelong therapeutic and preventive option among the two conditions.[5] However, the pivotal role of transfusion

Received: 16 October 2023
Accepted: 17 June 2024
Published: 24 June 2024

in SCD and thalassemia patients comes at the expense of significant consequences in these hyper-transfused patients, such as iron overload and RBC alloimmunization.[6]

Alloimmunisation associated with allogeneic RBC transfusion occurs due to exposure to non-self-immunogenic RBC antigens and the subsequent development of one or more alloantibodies by transfusion recipients.[6,7] The formation of antibodies against allogeneic RBC antigens can lead to several transfusion-associated adverse outcomes, such as acute and delayed hemolytic transfusion reactions (HTRs), hemolytic disease of foetus and the newborn (HDFN), and shortened RBC survival.[8] Additionally, it may be associated with the delayed provision of compatible blood units, which represents a challenge to both transfusion services and clinical teams and compromises patients' safety.[7]

The prevalence of RBC alloimmunisation in SCD and thalassemia patients shows great variations among different populations[9,10] with increased incidence due to racial differences.[11] In Saudi Arabia, several reports from different regions reported the rate of alloimmunization in SCD patients is up to 39.4% while in thalassemia patients is up to 35.57%.[12–17] This variability in the alloimmunisation rate appears to be associated with disparities in race, age, underlying clinical conditions and transfusion protocols.[9,18]

Jazan region, located on the coast of the Red Sea in the southwest corner of Saudi Arabia, is one of the regions with the highest prevalence of SCD and thalassaemia.[3,4] Patients with both disorders represent the largest group of patients who receive blood transfusions regularly. For the last 15 years, and to minimise the risk of alloimmunisation, the recommended transfusion protocol for patients with SCD or Thalassemia in the region has been the selection of RBC units that are extended-phenotype-matched for RhC, E, c, e, and K antigens, in addition to the standard matching for ABO and RhD types.[19] Furthermore, a recent study by Alsughayyir et al (2022) reported a gap between blood supply and the increased demand for blood for daily routine and emergency practices.[20]

Despite this fact, there was only one study investigating the effect of this practice on the prevalence and nature of alloimmunisation among these groups of patients[21] in this endemic area of hemoglobinopathies.[4] A single study in Jazan region reported that the rate of alloimmunization was 12.98% and autoimmunization was 0.52% among patients with SCD and the rate of alloimmunization was 13.21% and autoimmunization was 3.77% among patients with thalassemia.[21] In addition, it should be mentioned that a recent study reported that 55% of blood donors were Saudi and 45% otherwise among 4977 blood donors in Samtah-Jazan, which might impact the rate of alloimmunization in the region.[19,22] Furthermore, the incidence of A2 and A2B subgroups and anti-A1 antibody in the region has been linked to possible complications.[23]

Hence, we sought to look the rate of alloimmunisation in SCD and thalassemia patients in different hospitals of Jazan region, thus will provide in depth data for the improvement of blood transfusion protocol among SCD and thalassemia and report the finding to health care provided for more attention. Therefore, the aims of this study are to determine the prevalence of RBC alloimmunisation and associated antibody specificities among SCD and thalassemia patients from three major hospitals in Jazan region.

Materials and Methods

Study Population

This cross-sectional, multicenter retrospective study was conducted from January to December 2019 in the blood banks of three major Ministry of Health (MOH) hospitals in the Jazan region of Saudi Arabia – namely, King Fahd Central Hospital (KFCH) (n = 443 patients), Prince Mohammed Bin Nasser Hospital (PMBNH) (n = 350 patients) and Samtah General Hospital (SGH) (n = 234 patients). The study population (n = 1027 registered patients) comprised all patients with SCD and thalassemia registered in the blood banks of each of the three hospitals and transfused at least once during the study period.

Transfusion and Pre-Transfusion Testing Protocols

Hemoglobinopathy patients (including SCD and thalassemia patients) in the current study routinely received HbS-negative blood, leucocyte-reduced, non-irradiated and <14-day-old red cells that were Rh- and Kell-matched and compatible in the indirect antiglobulin (IAT) crossmatch. Patients who developed one or more alloantibodies were transfused with antigen-negative red cells, regardless of the persistence of previously detected alloantibodies. Before transfusing patients in these centers, blood samples were sent to the blood bank for determination of ABO/D grouping,

phenotyping for Rh and K antigens, antibody screening and identification of RBC antibodies using MOH-approved commercial column-agglutination technologies (Bio-Rad, Switzerland, and Ortho, USA) according to the manufacturer's instructions. Three-cell antigen panels were used for antibody screening testing. Antibody identification was then performed on patients whose blood samples tested positive for the presence of the RBC alloantibody.

Data Collection

Patient demographic and laboratory-result data were collected from the blood bank records of each participating hospital. The following data were collected for each transfused patient identified: diagnosis, gender, age, ABO and Rh groups, alloimmunisation status, and specificities of detected alloantibodies. The study included only SCD and thalassemia patients with alloimmunization and excluded other diseases.

The study was approved by the Jazan Research Ethics Committee in Jazan Directorate of Health Affairs, Ministry of Health (No. 021–2019).

Statistical Analysis

Statistical analyses were performed using Microsoft Excel 2016. Descriptive statistics were used to summarize and describe the collected data. The alloimmunisation rates were calculated as percentages for both genders and for the two patient groups. To determine if there were significant differences in the alloimmunisation rates between these groups, we employed the Chi-square test. P-values of less than 0.05 were considered statistically significant.

Results

Patients' Demographics

During the study period, a total of 1027 registered patients with hemoglobinopathy were identified to have received one or more transfusions. The demographic data of these patients are shown in Table 1.

Table 1 Demographics of Patients Included in the Study (n = 1027)

Variables		Number (%)
Gender	Male	483 (47.0)
	Female	544 (53.0)
Age in years	Median	15
	Range	1–48
Diagnosis	SCD	906 (88.2)
	Thalassemia	121 (11.8)
Blood Group	O	615 (59.9)
	A	305 (29.7)
	B	88 (8.6)
	AB	19 (1.8)
Rh type	Rh positive	981 (95.5)
	Rh negative	47 (4.5)
Antibody screening	Positive	78 (7.6)
	Negative	949 (92.4)

Alloimmunisation Rate

The antibody screen test was positive in 78 of the 1027 patients, who developed a total of 108 red-cell alloantibodies, giving an overall alloimmunisation rate of 7.6%. Demographic data for these patients are shown in Table 2. The rate of alloimmunisation in female patients was slightly higher than that of males (7.9% compared to 7.2%, respectively). However, this difference was found to be statistically insignificant (p = 0.69). Of the 906 patients diagnosed with SCD, 71 (7.8%) had one or more alloantibodies, while 7 (5.8%) patients of the 121 identified thalassemia patients developed alloantibodies. The alloimmunisation rate in the two patient groups did not differ significantly (p = 0.42).

Alloantibody Specificities

The proportion of the 78 alloimmunised patients who developed a single antibody was 78.2% (61 out of 78) with 54 patients in SCD and 7 patients in thalassemia. In SCD, out of the 54 patients, fifty-four (76%) with single alloantibody, seven (9.9%) with two alloantibodies and eight (11.3%) with three alloantibodies, while only two patients (2.8%) developed four antibodies (Table 2). In thalassemia, the 7 patients developed a single alloantibody, and none developed multiple antibodies (Table 2).

The detected single alloantibodies and their specificities are shown in Table 3. Two-thirds (80/108) of the alloantibodies detected in our study were found to be directed to antigens of the Rh (50.0%) and Kell (25.0%) blood-group systems. Anti-E and anti-K were the most prevalent antibodies (25.9% and 24.1%, respectively). The other commonly encountered antibodies were anti-c (13.0%), anti-C and unknown specificity (6.5% each), anti-Fy^a and anti-S (5.6% each). Among the 53 antibodies with Rh specificity, anti-D (1.9%), anti-e (0.9%), and anti-C^w (0.9%) were the lowest detected.

Table 4 presents the specificities of the multiple alloantibodies identified in SCD patients.

Table 2 Demographics of Identified Alloimmunised Sickle Cell Disease and Thalassemia Patients (n = 78)

Variable		Total Number (%)	SCD Number (%)	Thalassemia Number (%)
Number of patients (%)		78 (100)	71 (91.0)	7 (9.0)
Gender	Male	35 (44.9)	31 (43.7)	4 (57.1)
	Female	43 (55.1)	40 (56.3)	3 (42.9)
Age in years	Median	24.5	25	12
	Range	7–42	7–42	10–24
ABO Blood group	O	46 (59.0)	45 (63.4)	1 (14.3)
	A	24 (30.8)	20 (28.2)	4 (57.1)
	B	4 (5.1)	2 (2.8)	2 (28.6)
	AB	4 (5.1)	4 (5.6)	0 (0)
Rh type	Rh positive	73 (93.6)	69 (97.2)	4 (57.1)
	Rh negative	5 (6.4)	2 (2.8)	3 (42.9)
Number of alloantibodies	Single	61 (78.2)	54 (76.0)	7 (100)
	Two	7 (9.0)	7 (9.9)	0 (0)
	Three	8 (10.2)	8 (11.3)	0 (0)
	Four	2 (2.6)	2 (2.8)	0 (0)

Abbreviation: SCD, sickle cell disease.

Table 3 Type and Frequency of Alloantibodies Identified in Sickle Cell Disease and Thalassemia Patients (Total of 108 Antibodies in 78 Patients)

Antibody	Total Number (%)	SCD Number (%)	Thalassemia Number (%)
Anti-E	28 (25.9)	27 (26.7)	1 (14.3)
Anti-K	26 (24.1)	25 (24.8)	1 (14.3)
Anti-c	14 (13.0)	13 (12.9)	1 (14.3)
Anti-C	7 (6.5)	7 (6.9)	0 (0)
Unidentified specificity	7 (6.5)	5 (5.0)	2 (28.6)
Anti-Fy^a	6 (5.6)	5 (5.0)	1 (14.3)
Anti-S	6 (5.6)	6 (5.9)	0 (0)
Anti-Jk^a	5 (4.6)	5 (5.0)	0 (0)
Anti-D	2 (1.9)	2 (2.0)	0 (0)
Anti-Kp^a	1 (0.9)	1 (1.0)	0 (0)
Anti-Lu^a	1 (0.9)	1 (1.0)	0 (0)
Anti-e	1 (0.9)	1 (1.0)	0 (0)
Anti-C^w	1 (0.9)	0 (0)	1 (14.3)
Anti-Fy^b	1 (0.9)	1 (1.0)	0 (0)
Anti-M	1 (0.9)	1 (1.0)	0 (0)
Anti-Ch/Rg	1 (0.9)	1 (1.0)	0 (0)
Total	**108 (100)**	**101 (93.5)**	**7 (6.5)**

Abbreviation: SCD, sickle cell disease.

Discussion

In the present study, the overall prevalence of alloimmunisation was 7.6%, with rates of 7.8% and 5.8% in SCD and Thalassemic patients, respectively. This is considerably lower than those reported from a single center in Jazan region and other regions of Saudi Arabia (Table 5), where the alloimmunisation rates were found to be 12.98% in Jazan region,[21] 12.8–39.4% in the Western region,[13,14] 22.06% in Riyadh,[15] and 13.7% in the Eastern region,[16] but comparable to the rate of alloimmunization reported from Al-Madinah city.[17] Additionally, a recent study conducted in the Western region reported rates of 39.42% and 35.57% in SCD and thalassemia patients, respectively. Another study in 2023 from Al-Hasa, eastern region of Saudi Arabia, reported 16.7% alloimmunization for SCD patients and 11.97% alloimmunization for thalassemia patients.[12] The rate of alloimmunisation reported from the latter two studies from the western region is significantly higher when compared to our study.[12,14] High alloimmunisation rates reported previously from Jazan region[21] might be due to the fact that the study was from single center and had lower sample size than the current study.[21] In addition, the differences from the other in these studies in Saudi Arabia could be attributed to the diverse ethnic backgrounds of the donor and recipient populations and multiple transfusion of non-phenotypically matched blood units, which are both known to be associated with an increased risk of alloimmunisation in transfusion-dependent patients.[6] In addition, the field of transfusion practice and services is improving dramatically in Saudi Arabia since the introducing several national initiatives by the ministry of health including accreditation process and clear guidelines.[24] In addition, the availability of staff continuous programs on Blood banking and transfusion sciences.[25]

Table 4 Type and Frequency of Multiple Alloantibodies Identified in SCD Patients (Total of 17 Multiple Antibodies in 71 SCD Patients)

Number of Antibodies	Type of Antibody	SCD Number (%)
Two antibodies	Anti-E+ anti-K	2
	Anti-E+ anti-c	1
	Anti-C+ anti-E	1
	Anti-C+ anti-Jk[a]	1
	Anti-K+ anti-Fy[a]	1
	Anti-M+ anti-S	1
	Total	**7 (9.9)**
Three antibodies	Anti-E+ anti-Kpa + anti-Lua	2
	Anti-E+ anti-K + anti-S	2
	Anti-C+ anti-E + anti-K	1
	Anti-E+ anti-c + anti-Fya	1
	Anti-E+ anti-Jka + anti-Fya	1
	Anti-E+ anti-S + anti-Lua	1
	Total	**8 (11.3)**
Four antibodies	Anti-C+ anti-E+ anti-K + anti-Jka	1
	Anti-c+ anti-Fya+ anti-Fyb+ anti-S	1
	Total	**2 (2.8)**

Abbreviation: SCD, sickle cell disease.

Table 5 Frequency of Alloimmunization Rate Reported in Literature in Saudi Arabia and Worldwide

Study Site	Year (Period of the Study)	Sample Size	Overall Alloimmunization SCD+Thalassemia	Alloimmunization SCD	Alloimmunization Thalassemia	Ref
Riyadh city	1993–2006	68	22.06%	NR "	NR "	[15]
Eastern province	1996–2004	350	NR "	13.7%	NR "	[16]
Western province – Jeddah city	2010–2016	219	NR "	17.8%	NR "	[13]
Jazan province	2014–2017	438	NR "	12.98%	13.21%	[21]
Western province – Jeddah city	2017–2018	208	NR "	39.42%	35.57%	[14]
Jazan province	2019	1027	7.6%	7.8%	5.6	Current study
Eastern province - Alhasa city	2022	364	12.98% *	16.7%	11.97%	[12]
Oman	NS ¥	262	25.95% *	31.6%	20%	[26]

(*Continued*)

Table 5 (Continued).

Study Site	Year (Period of the Study)	Sample Size	Overall Alloimmunization SCD+Thalassemia	Alloimmunization SCD	Alloimmunization Thalassemia	Ref
Kuwait Grp 1	NS ¥	233	NR "	65.5%	NR "	[27]
Kuwait Grp 2			NR "	23.6%	NR "	
Egypt	2008–2009	235	NR "	NR "	19.5%	[28]
Sudan	2017–2018	31	NR "	29.0%	NR "	[29]

Note: *Calculated percentage by the authors.
Abbreviations: " NR, not reported; ¥ NS, not specified.

When compared to other neighboring countries, the observed alloimmunisation rate in our population is significantly lower than those reported by several studies conducted, for instance, in Oman (31.5%), Kuwait (23.6%), Egypt (19.5%) and Sudan (22.7%)[26–29] (Table 5). On the contrary, lower rates of alloimmunisation similar to that reported in this study were reported from several African countries ranging from 2.6% to 10%, which describe a lower rate of alloimmunisation when more racial homogeneity between the donors and recipients is available.[30,31]

The lower rate of alloimmunisation reported in this study could be explained by the routine transfusion of extended phenotypic matched RBC to all registered patients in the study centers, which comprises matching for C, c, E, e and K antigens, in addition to ABO and D. It has been shown from various studies that matching for E, C and K reduced the risk of alloimmunisation significantly.[32,33] Further extensive matching for other clinically significant antigens, including Duffy, Kidd and MNS, is even more efficient in reducing alloimmunisation among SCD patients.[34] This option, however, is often not practical in most cases due to a scarce blood supply.[6] Hence, our findings suggest an effective adherence by the participating blood banks to the provision of Rh and K phenotypically matched blood to SCD and thalassemia patients.

Despite the documented diversity of blood donors in Saudi Arabia,[14] our study suggests that the lower rate of alloimmunization in our sample could be attributed to a certain level of homogeneity among donors and recipients within the Jazan population. The racial or ethnic backgrounds amongst donor and recipient populations form an initial trigger of alloimmunisation.[6,35] Thus, a lower rate of alloimmunisation is predictable among the more homogenous population.[18] In fact, the homogeneity between donors and recipients in Greece and Italy played a crucial role in reducing alloimmunisation rates.[36,37] Similarly, low rates have also been reported in more homogenous populations from African populations in Uganda[30] and populations in Jamaica.[38] Conversely, higher rates of alloimmunisation were reported in populations with more heterogenous donor and patient groups.[39,40] Nonetheless, further studies to assess the actual degree of donor-patient homogeneity in our population and its association with the risk of alloimmunisation are still required.

The association of the female sex with an increased risk of RBC alloimmunisation has been demonstrated by several studies.[27,41] In our study, however, we did not find a significant difference in the rate of alloimmunisation between female and male patients (7.9% and 7.2%, respectively; $p = 0.69$). This finding is in line with previous findings of other researchers, who reported no associations between sex and rate of alloimmunisation.[42] The observed lack of association in our study between female sex and alloimmunisation may be the result of the overall low rate of alloimmunisation in our population, and therefore, further studies with a larger sample size would be needed to confirm this finding.

When the specificity of alloantibodies was analysed, we found that two-thirds (80/108) of the identified RBC alloantibodies in our study population were against antigens in the Rh (48.1%) and the K (26.9%). Anti-E and anti-K alloantibodies were found to be the most frequent, representing 25.9% and 24.1% of the antibodies, respectively, which agrees with the data reported by other researchers.[13,18,39] This finding is particularly important since these antibodies were detected in our patients, despite the routine transfusion of Rh and K phenotypically matched RBC. Several factors likely contribute to this finding. Firstly, alloimmunisation to these antigens could be the result of a failure to transfuse phenotypically matched RBC. This might occasionally occur when some patients are transfused outside our centers, where phenotype-matched blood is not given, or because of shortages of antigen-negative red cell units, particularly in

conditions requiring urgent transfusion.[35] Such situations remain ongoing challenges for our blood banks and place patients at risk of receiving unmatched phenotypic blood and subsequent alloimmunisation. An additional reason for alloimmunisation is the inaccurate identification and reporting of RBC phenotypes in recently transfused patients with partially mismatched blood. Although several laboratory techniques are employed to develop serological phenotypes, they are laborious and time-consuming and inaccurate.[43,44] More importantly, genetic diversity in the Rh blood-group system further complicates accurate phenotyping using serological methods due to various partial antigens and variants in the Rh system.[45] Patients with altered RH alleles and other blood-group variants can be inaccurately typed as antigen-positive by serologic methods, and when transfused, they often produce immune antibodies against antigenic epitopes they lack.[7] The detectable anti-D antibodies in our study may indeed represent anti-D in the context of RHD gene variants. Understanding the prevalence and impact of RHD gene variants is essential, as they may contribute to the production of anti-D antibodies and complicate transfusion compatibility. For this reason, molecular genotyping for transfusion-dependent recipients has been implemented in several developing countries, which has proven effective in reducing alloimmunisation.[46]

Our present study is significant since it is the first multicenter study to assess the magnitude of red-cell alloimmunisation in SCD and thalassemia patients in the Jazan region who are routinely transfused with Rh and K phenotypically matched blood. The rate of alloimmunisation in our study population is amongst the lowest rate posted in other parts of Saudi Arabia or other neighbouring countries. This finding gives additional evidence for the effectiveness of routine transfusion of phenotypically matched red-cell units to patients at a higher risk of alloimmunisation. Implementing additional strategies, such as molecular blood grouping and a unified patient electronic database, can further reduce the risk of alloimmunisation.

Limitations of the Study

The current study has some limitations including possible omission of weak or short-lived alloantibodies that may appear within a week of transfusion and then quickly become undetectable by the next antibody screen. Due to the difficulty in accessing the data in blood bank records, our study did not address the age at which patients were first transfused and the number of units transfused as independent factors for alloimmunisation. In addition, although the current study observed a lack of association between female sex and alloimmunisation, it is important to acknowledge the potential limitation of underpowering due to the overall low rate of alloimmunisation. Moreover, the clinical details of each of hemoglobinopathies should be considered and compared. Therefore, further studies with larger sample sizes are warranted to confirm and strengthen our findings.

Conclusion

The current study showed prevalence of RBC alloimmunisation among transfusion-dependent SCD and thalassemia patients in the Jazan region of Saudi Arabia, where the two disorders are common. This study will aid in building a database for the most encountered antibodies in SCD and thalassemia, which will help in selecting the most appropriate antigen-negative red cells. It also supports our current transfusion practice of selecting Rh and K-matched RBC for multi-transfused patients. Patients' knowledge regarding the risk of alloimmunisation is crucial when a specific phenotype is required, as it helps ensure informed decision-making and adherence to protocols for safe transfusion practices. Transfusion information cards are currently recommended to provide information when transfusion support is most likely to occur, especially on the occasion of a particular transfusion specification. More research is needed to identify other factors associated with the residual risk of alloimmunisation in our patients with SCD and thalassemia. Furthermore, the study articulates the rate of RBC alloimmunisation among SCD and thalassemia patients in the Jazan region and proposes practical applications for the findings, such as the creation of a database for antibodies and the continuation of Rh and K-matched transfusion practices not only in Jazan region but on national levels.

Institutional Review Board Statement

The study was approved by the Jazan Research Ethics Committee in Jazan Directorate of Health Affairs, Ministry of Health (No. 021-2019).

Informed Consent Statement

Signed informed consents were obtained from the adult study participants or from children's guardians. The study was carried out according to the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

The authors declare no conflicts of interest in this work.

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