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Frequencies of RhCE and Kell phenotypes in Xinjiang using a cross–minorities transfusion simulation model

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ABSTRACT

Xinjiang represents one of the richest minorities´ areas in China. This high ethnic diversity reflects in the blood groups and immune status and has a consequent impact on blood transfusions. To evaluate the risks of cross–minority transfusion in Xinjiang, we investigated the frequencies of erythrocytic Rh and K antigens among 1,073 Uyghurs and 213 Kazaks. We further reviewed the literature on the frequency of erythrocytic antigens to develop a simulation model for calculating the risk of patients in Xinjiang exposed to mismatched erythrocytic antigens. The frequencies of RhE, RhC, and K phenotypes were as follows: C antigen, 52.3% in Uyghurs and 56.8% in Kazaks; c antigen, 47.7% in Uyghurs and 43.2% in Kazaks; E antigen, 25.5% in Uyghurs and 27.2% in Kazaks; e antigen, 74.5% in Uyghurs and 72.8% in Kazaks; K antigen, 1.8% in Uyghurs and 1.8% in Kazaks. The population–adjusted cumulative match rate demonstrated that 53.3%, 51.4%, 50.6%, and 53.7% of the Uyghur, Kazak, Han, and Hui populations were recipients, respectively, although the recipients were transfused with an unknown Rh blood type. We concluded that the risks of cross–minority transfusion in Xinjiang are insignificant. The best strategy appears to be K and Rh–matched transfusions in this region due to the much higher frequency of the K antigen compared toother areas in China.

Keywords: Kell(K) blood type, Rh(CE) blood type, Uyghur, Kazak, antigen distribution

INTRODUCTION

Xinjiang is the one of the richest minority areas in China with over 13 ethnicities living in various areas, including Han, Hui, Uyghur, Manchu, Kirgiz, Tajik, Xib, Ozbek, Russian, Tatar, Mongolian, Kazak, and Daur. According to the 6th China Census conducted in 2010, four ethnicities represented over 95% of the population in Xinjiang, these were 11.27 million Uyghurs(48.53%), 8.60 million Hans(37.01%), 1.60 million Kazaks(6.88%), and 1.06 million Huis(4.56%)[1].

Recent studies confirmed that red blood cell(RBC) allo–antibodies against the Rh system were the major allo–antibodies in China[2]. Several studies have demonstrated a high diversity in the frequency of RBC allo–antibodies among Hans and Uyghurs[3]. Moreover, the numbers of antibodies against Asian–specific high–frequency antigens, including Fy^a, and low–frequency antigens such as K are reported to be notably high in Xinjiang[3–4]. Although the frequencies of blood groups, including ABO, Rh, Kidd, and MNS in

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Xinjiang have been reported, some blood groups have still as yet not beeninvestigated in this region, including the Kell system and anti–K, which are known to show a higher prevalence in Xinjiang compared to that in Beijing[4]. Despite the ethnic diversity of blood groups however, and their potential immune responses impact on transfusion, few studies have evaluated the status of cross–minorities´ transfusions in Xinjiang.

To evaluate the risks of cross–minority transfusions in Xinjiang, we investigated the frequencies of erythrocytic Rh and K antigens among the major minority groups: Uyghurs and Kazaks.We further reviewed the literature to obtain the reported frequencies of erythrocytic antigens, which were used to conduct a simulation study for determining the risk of exposure to mismatched erythrocytic antigens for patients in Xinjiang.

MATERIALS AND METHODS

Study population

The subjects enrolled in our study were recruited from two medical centres, Xinjiang Uyghur Autonomous People' s Hospital and the Affiliated Hospital of Traditional Chinese Medicine of Xinjiang Medical University, between June 2016 and December 2016. Subjects with a history of transfusion in the last three months or auto–controlled reported positive specimens were excluded. For subjects that had been admitted at either or both of the medical centres several times during the period of the study, only the data from the first report were recorded. Overall, 1,073 Uyghurs, including 529 males (49.3%) and 544 females (50.7%), and 213 Kazaks, including 96 males (45.1%) and 117 females (54.9%),were included in the study and phenotyped for RhCE and Kell. The age ranges were 5 days to 85 years in Uyghurs and 12 days to 78 years in Kazaks.

To calculate the risks of exposure to mismatched erythrocytic antigens for the patients in Xinjiang, we reviewed available studies[5,6]. The reported frequencies of RhCE phenotypes were as follows: 45.1% CCee, 1.9% CCEe, 0.0% CCEE, 9.1% Ccee, 26.6% CcEe, 3.8% CcEE, 1.9% ccee, 2.4% ccEe, and 9.1% ccEE in Hans; 33.0% CCee, 1.3% CCEe, 0.2% CCEE, 14.7% Ccee, 31.2% CcEe, 3.4% CcEE, 1.8% ccee, 8.3% ccEe, and 6.2% ccEE in Kazaks; 31.1% CCee, 2.2% CCEe, 0.2% CCEE, 19.1% Ccee, 25.4% CcEe, 1.8% CcEE, 3.0% ccee, 8.1% ccEe, and 8.9% ccEE in Uyghurs; and 37.1% CCee, 6.0% CCEe, 0.4% CCEE, 9.2% Ccee, 30.7% CcEe, 1.2% CcEE, 2.0% ccee, 5.2% ccEe, and 8.4% ccEE in the Hui minority.

Phenotyping

Three millilitres of peripheral venous blood was drawn from each subject and placed in EDTA–Na_2 tubes. The phenotyping methods included a micro–beads test for RhCE and K antigen performed on an automated machine (ORTHO Workstation, AutoVue, Ortho Clinical Diagnostics, UK). In addition, the samples were incubated with monoclonal antibodies against the erythrocytic antigens anti–C, anti–c, anti–E, anti–e (Shanghai blood Biological Medicine Co Ltd., Shanghai, China), and anti–K (Sunquin GmbH, Switzerland). In brief, EDTA–whole blood was centrifuged at 1,000*g* for 5 min (KUBOTA KA–2200, Japan) and 1 mL of packed RBCs was pipetted and centrifuged at 800*g* for 1 min(KUBOTA MC–450, Japan); the procedure was repeated three times. Ten microliters of the washed packed RBCs was dissolved into 1 mL of 0.9% normal saline at a concentration of 0.8%–1.0%. The RBC suspension was examined with Rh/K micro–bead phenotyping kits (Rh/K blood group diagnostic reagent card, Ortho BioVue System, Ortho Clinical Diagnostics, UK). For the tube method of analysis, 3% of the washed RBCs were reacted with 100 μL of the monoclonal antibody by incubating at room temperature for 10 min,and a positive K phenotype was judged when the titre of any phenotype was lower than 3+. The other procedures such as antibody screening, sample reception, report documentation, and report writing were all based on regulations and the standard procedures specified by the transfusion departments of the two medical centres.

Statistical analysis

For the frequencies of *RHCE* alleles based on the RhCE phenotyping results, the chi–squared test was used to determine the fit to Hardy–Weinberg equilibrium. Differences between groups with a two–sided $P < 0.05$ were considered statistically significant. All statistical analyses were conducted using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Frequencies of RhCE phenotypes and alleles in Kazaks and Uyghurs

The frequencies of *RHCE* alleles in Uyghurs were as follows: 26.6% CCee, 0.4% CCEe, 0.1% CCEE, 21.8% Ccee, 28.4% CcEe, 0.4% CcEE, 6.9% ccee, 9.6% ccEe, and 5.9% ccEE, representing an insignificant difference (P=0.999) from previously reported values. The frequencies of *RHCE* alleles in Kazaks were as follows: 34.7% CCee, 0.5% CCEe, 0.0% CCEE, 16.4% Ccee, 26.8% CcEe, 0.0% CcEE, 4.7% ccee, 6.6% ccEe, and 10.3% ccEE, also representing an insignificant difference (P=1.000) with the pre–

viously reported results ***(Table 1)***. The chi–squared test confirmed that the distribution of *RHCE* alleles in Uyghurs and Kazaks were in line with the Hardy–Weinberg equilibrium.

The frequencies of the RhC, RhE, and K phenotypes in Uyghurs were 52.3% C antigen and 47.7% Cantigen of RhC; 25.5% E antigen and 74.5% e antigen of RhE; and 1.8% K antigen of Kell. The frequencies of RhC, RhE, and K phenotypes in Kazaks were 56.8% C antigen and 43.2% c antigen of RhC; 27.2% E antigen and 72.8% e antigen of RhE; and 1.8% K antigen of Kell ***(Table 2)***.

Table 1 **Frequencies of *RhCE* alleles in Uyghurs and Kazaks**

Allele	Uyghurs (*n*=1,073)				Kazaks (*n*=213)			
	Our study		Previous	*P*	Our study		Previous	*P*
	n	%	study/%		*n*	%	study/%	
CCee	285	26.6	31.1	0.999	74	34.7	33.0	1.000
CCEe	4	0.4	2.2		1	0.5	1.3	
CCEE	1	0.1	0.2		0	0.0	0.2	
Ccee	234	21.8	19.1		35	16.4	14.7	
CcEe	305	28.4	25.4		57	26.8	31.2	
CcEE	4	0.4	1.8		0	0.0	3.4	
ccee	74	6.9	3.0		10	4.7	1.8	
ccEe	103	9.6	8.1		14	6.6	8.3	
ccEE	63	5.9	8.9		22	10.3	6.2	

Table 2 **Frequencies of RhCE and Kell phenotypes in Uyghurs and Kazaks**

Phenotype	Uyghurs		Kazaks	
	frquency	%	frquency	%
RhC				
C	1,122	52.3	242	56.8
c	1,024	47.7	184	43.2
RhE				
E	547	25.5	116	27.2
e	1,599	74.5	310	72.8
Kell				
K^+ (Kk/KK)	19	1.8	4	1.8

Rate of Rh–type compatibility between recipients and donors for minorities

According to the frequencies of *RHCE* alleles in minorities living in Xinjiang, the rates of compatibility for patients with any Rh type among Xinjiang transfusion donors are shown in ***Table 3***. Considering the minorities acting as recipients, the patients that received transfused blood from donors of Han ethnicity showed the highest cumulative match rate among the four major minorities in Xinjiang. The population–adjusted cumulative match rates were 53.3%, 51.4%, 50.6%, and 53.7% for Uyghurs, Kazaks, Hans, and Huis as recipients. The recipients transfused with blood of an unknown Rh type and demographic composition based on the 6th China Census of 2010, were included as adjusted parameters ***(Table 4)***.

DISCUSSION

In this study, we determined the frequency of *RHCE* alleles and phenotypesof RhCE and the K antigen, and combined data from previous studies to analyze the transfusion–compatible rate with respect to RhCE matching for evaluating the risk of cross–

Table 3 **Patients of different Rh types in Xinjiang transfused with Rh–compatible blood from minorities (%)**

Recipient	Donor								
	CCee	CCEe	CCEE	Ccee	CcEe	CcEE	ccee	ccEe	ccEE
Alleles									
CCee	Compatible	Compatible		Compatible	Compatible				
CCEe		Compatible			Compatible				
CCEE		Compatible	Compatible		Compatible	Compatible			
Ccee				Compatible	Compatible				
CcEe					Compatible				
CcEE					Compatible	Compatible			
ccee				Compatible	Compatible		Compatible	Compatible	
ccEe					Compatible			Compatible	
ccEE					Compatible	Compatible		Compatible	Compatible
Minorities									
Hans	45.1	47.0	0.0	56.1	100.0	12.9	1.9	13.4	9.1
Kazaks	34.7	35.2	0.0	55.8	100.0	10.3	4.7	21.6	10.3
Uyghurs	26.6	27.1	0.1	55.3	100.0	6.4	6.9	22.4	5.9
Huis	37.1	43.4	0.4	48.2	100.0	10.0	2.0	15.5	8.4

The frequency of RhCE in monorities from our investigation and present study were regard as donor to offer the RhCE–match blood for recipients.

Table 4 **Cumulative match rate between minorities as recipients and donors (%)**

Donor	Recipient			
	Uyghurs	Kazaks	Hans	Huis
Hans	54.8	53.8	54.7	57.0
Kazaks	53.0	50.9	50.0	52.9
Uyghurs	50.7	47.7	45.6	49.1
Huis	51.1	49.7	50.1	53.1
Population–adjusted cummulative match rate	53.5	51.4	50.6	53.7

Population–adjusted cumulative match rates were based on the minorities rate as an adjusted parameter according to the 6th China Census of 2010.

minorities´transfusion[3].

The frequencies of blood groups show diversity among races and areas. The prevalence of K antigen in the Kell blood groups was reported to be 0.02%–0.48% in Japan, 5.68% in Indian blood donors, 9.8% in Caucasians, and 2% in Black donors[7–8]. In China, the prevalence of Chinese blood donors in Shanghai was reported to be 0.06%, and the genotyping prevalence in the Huis and Uyghurs was 1.36% and 3.16%, respectively, in Xinjiang[9–10]. Evers and Schonewille *et al*.[11–12] demonstrated donor–recipient RBC matching strategies will be most efficient when primarily focusing on the prevention of C, c, E, K, and Jk(a) alloimmunisation. Given that K shows adominant pattern of inheritance, the offspring from ethnic intermarriage between Hans and minorities can result in anti–K–related haemolytic disease in newborns; therefore,the risks of cross–minorities´ transfusion should be carefully considered[12]. A strategy of Rh and K–matched transfusion may be possible because of the high K prevalence in Xinjiang, which is higher than that of populations in central China. In addition, the presence of anti–K has also been reported in Xinjiang.

According to the simulated model, it is easier to find compatible blood from Hans for patients who reported RBC allo–antibodies in Xinjiang with CCee, CCEe, Ccee, and CcEE alleles. In addition, Kazak patients with ccEE, Uyghur patients with ccee and ccEe, and Hui patients with CCEE have a greater chance to find compatible blood than others of the same minorities. These conclusions are also supported by the ethic polymorphism of RBC blood groups, because of a previous government policy forcing Hans to migrate to Xinjiang around 100 years ago. Our simulation model indicates that cross–minority transfusion does not have a significant risk, and that Hans are the most appropriate blood donors regardless of the recipient minority type found in Xinjiang when the RhCE type of the recipients and donors are unknown.

Overall, we conclude that there is an insignificant risk of cross–minority transfusion in Xinjiang, and the best strategy is to perform K and Rh–matched transfusion in Xinjiang due to the much higher frequency of the K antigen in this region compared to other districts in China.

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