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Original Article

혈액질환 환자에서 관찰된 적혈구 동종면역의 특성

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Characteristics of Red Blood Cell Alloimmunization in Patients with Hematologic Diseases

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Background: Patients with hematologic diseases receive frequent transfusions of red blood cells (RBCs), platelets (PLTs), and fresh frozen plasma (FFP). These patients are more likely to develop alloimmunization due to repeated exposure to RBC antigens. The purpose of this study was to investigate the need for extended RBC matching in patients with hematologic diseases and a history of repeated transfusions.
Methods: We assessed patients who had undergone bone marrow examination at the Dong-A University hospital, Busan, South Korea from January 2008 to December 2012. A total of 571 patients were examined. We retrospectively investigated the frequency and volume of the transfusions of RBCs, PLTs, and FFP, the diagnosis of each patient, and the generation of unexpected antibodies.
Results: Alloimmunization occurred in 18 out of 571 patients (3.15%). Among the identified antibodies, Rhesus (Rh) group antibodies were the most frequently detected (58.6%). The number of RBC transfusion episodes was higher in the alloimmunized group than that in the non-alloimmunized group (P=0.0016). The RBC transfusion volume was also significantly higher in the alloimmunized group than that in the non-alloimmunized group (P=0.0020). Also, the number of PLT transfusion episodes and transfusion volume were higher in the alloimmunized group. There were no statistically significant differences in the sex, age, or FFP transfusions between the two groups.
Conclusion: The number of RBC transfusion episodes and the RBC transfusion volume affected the possibility of generating unexpected antibodies. The number of PLT transfusion episodes and the PLT transfusion volume also affected alloimmunization. The Rh antigen should therefore be matched in elderly patients who are expected to receive repeated blood transfusions. **(Korean J Blood Transfus 2022;33:14-23)**

Key words: Unexpected antibody, Alloimmunization, Extended RBC matching

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Introduction

Red blood cell (RBC) alloimmunization is an important complication in chronically transfused patients [1]. Alloimmunization is commonly associated with repetitive transfusions and can lead to a risk of delayed hemolytic reactions [2]. Studies suggest that 1～7% of transfused patients will produce alloantibodies [3,4].

In previous studies, several factors have been shown to increase the risk of RBC alloimmunization. These include age, sex, disease type, transfusion volume, and human leukocyte antigen (HLA) allele [5-8]. For example, a study found that myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMML) patients had a higher incidence of alloimmunization [5]. A different study showed that women beyond the childbearing age had a higher risk of alloimmunization [6]. Also, another study reported that the HLA-DRB1 phenotype was associated with the presence of alloantibodies [7]. On the other hand, leukemia and lymphoma patients taking immunosuppressants had a lower rate of alloimmunization [8]. Further, a Korean study showed that the cumulative risk of alloimmunization was higher in liver cirrhosis than in MDS patients [9].

In a Canadian study, prophylactic Rhesus (Rh) and Kell (K) antigen matching in MDS patients reduced the rate of alloimmunization [10]. The Dutch blood transfusion guidelines recommend performing extended Rh and Kell antigen matching in some disease groups and patient populations prior to transfusions [11]. However, in Korea, other than ABO and Rh-D antigen matching, which are done routinely, only a few institutions conduct additional RBC antigen tests.

Patients with hematologic diseases often require frequent transfusions of RBCs, fresh frozen plasma (FFP), and platelets (PLTs). These patients are more likely to experience alloimmunization due to repeated exposure to foreign RBC antigens [12]. When this happens, delayed hemolytic transfusion reactions (DHTR) may occur, and it can be difficult to find suitable blood donors.

The types of alloantibodies differ by race and ethnicity, so additional studies specific to the Korean population are needed [13]. The purpose of this study was to investigate the need for extended RBC matching in Korean patients with hematologic diseases and a history of repeated transfusions. In this study, we analyzed the characteristics of the alloimmunized group and the association between age, sex, disease type, number of transfusion episodes and transfusion volume, and the development of alloimmunization.

Materials and Methods

We reviewed the clinical and transfusion records of patients who had undergone bone marrow (BM) examinations at the Dong-A University Hospital, Busan, South Korea from January 2008 to December 2012. Data on the transfusion history and antibody identification tests performed up to June 2016 were analyzed. The total number of BM examinations performed was 1,458, and there were 910 patients, excluding duplicated patients. A total of 339 patients were excluded from the study (Fig. 1).

1. Exclusion criteria

1. Patients with non-hematologic diseases, such as liver cirrhosis, infections, solid tumors, systemic lupus erythematosus, and others (98 patients).

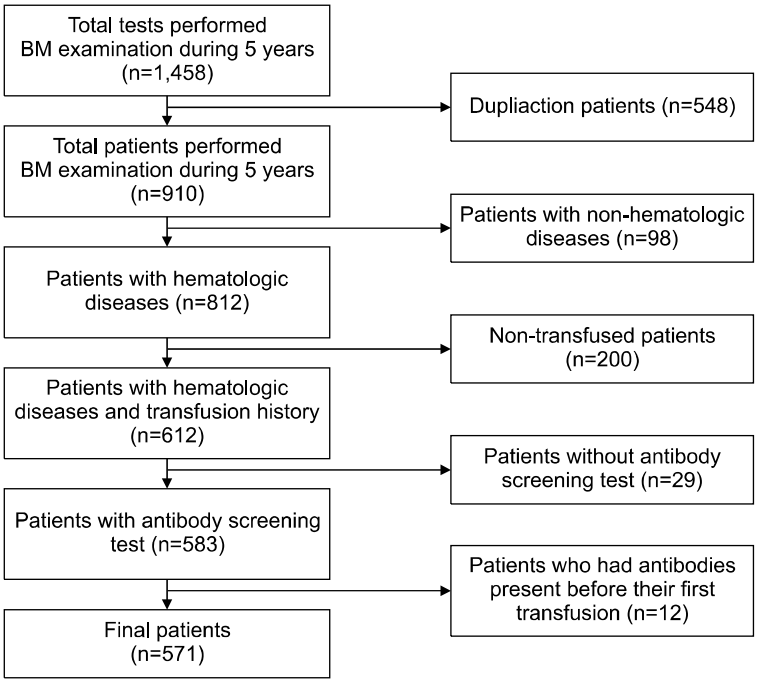

Fig. 1. Flow chart showing the process of patient selection.

2. Non-transfused patients with hematologic diseases (200 patients).
3. Patients who were not given antibody screening tests because they received only PLT transfusions (29 patients).
4. Patients who had alloantibodies or autoantibodies before their first transfusion (12 patients).

The total number of examined patients was 571. First, these patients were divided into 9 groups according to their disease type. The nine groups were: 1) aplastic anemia (AA), 2) acute myeloid leukemia (AML), 3) acute lymphoblastic leukemia (ALL), 4) myeloproliferative neoplasm (MPN), 5) MDS and CMML, 6) lymphoma and chronic lymphocytic leukemia (CLL), 7) multiple myeloma (MM), monoclonal gammopathy of undetermined significance (MGUS) and plasma cell leukemia (PCL), 8) idiopathic thrombocytopenic purpura (ITP), and 9) other hematologic diseases.

All patients were separated into two main groups: the alloimmunized and the non-alloimmunized groups. Then, the age and sex of the patients in the two groups were compared. Also, the number of transfusion episodes and the transfusion volumes of RBCs, PLTs, and FFP were calculated for each group. A transfusion volume of 1 unit was equivalent to 400 mL of RBCs, FFP or PLTs. In the alloimmunized group, we investigated the age, sex, disease group, transfusion history, type of alloantibodies, and the period between antibody detection and the last transfusion. The alloimmunization rate and the transfusion characteristics of the members of the 9

disease groups were analyzed and compared.

Lastly, we made a group comprising of non-alloimmunized patients who received more than 25 units of RBCs, researched its characteristics, and compared it with the other groups.

Data were collected from a review of hospital charts and the hospital transfusion service registrations. A hospital chart review was performed to get information about the patients' age, sex, disease type, and type of alloantibodies. Transfusion history, including the number of transfusion episodes and transfusion volume, was obtained from the hospital transfusion service registrations.

Antibody screening and identification tests were performed using the LISS/Coombs gel assay and NaCl/Enzyme assay (DiaMed AG, Cressier sur Morat, Switzerland). Antibody identification tests were carried out if the antibody screening test was positive. The test was performed using 11 known cells and could detect Rh, Kell, Duffy, Kidd, Lewis, P1Pk, MNS, Lutheran, and Xg blood group antigens.

The statistical analysis was performed using MedCalc for Windows, version 12.7.0.0 (MedCalc Software, Ostend, Belgium). A two-sided *P*-value of less than 0.05 was regarded as significant. All the results were expressed as medians with 95% confidence intervals (CI) or numbers with percentages. A Mann-Whitney U test was used for the comparison of non-normally distributed data. Chi-squared tests were used to calculate the statistical differences between groups. A Kruskal-Wallis test was also used to compare the groups. In addition, some factors associated with the incidence of alloimmunization were evaluated using multiple logistic regression analysis.

Results

The total number of patients who participated in this study was 571. The number of patients in the alloimmunized group was 18, and 553 patients were in the

Table 1. Baseline characteristics and transfusion history of the two groups in the study population

Variables	Total Patients (N=571)	Alloimmunization		*P*-value
		No (N=553)	Yes (N=18)	
Age (years)	60.0 (58.6～62.0)	60.0 (58.0～62.0)	61.5 (55.2～71.0)	0.4607
Male, N	306 (53.6)	297 (53.7)	9 (50.0)	0.9440
RBC (units)				
Number of transfusion episodes	8.0 (7.0～9.0)	7.0 (6.0～9.0)	17.5 (10.0～26.0)	0.0016
Units or transfusion volume	14.8 (13.0～17.0)	14.0 (12.6～16.6)	37.1 (20.5～48.3)	0.0020
PLT (units)				
Number of transfusion episodes	7.0 (5.0～9.0)	7.0 (5.0～8.0)	19.5 (8.6～42.6)	0.0269
Units of transfusion volume	49.6 (37.2～64.3)	46.2 (35.0～61.4)	122.8 (69.4～297.2)	0.0249

1 unit is 400 mL of RBCs, FFP, PLTs.
Apheresis-PLT is calculated in units of 5.
Data are shown as median (95% confidence interval) or number (percentage).
Abbreviations: RBCs, red blood cells; FFP, fresh frozen plasma; PLTs, platelets.

non-alloimmunized group. The alloimmunization rate of patients with hematologic diseases was 3.15%.

The characteristics of the two groups were compared. The baseline characteristics and transfusion history of the two groups are summarized in Table 1. There were no significant differences between the two groups with regard to age and sex. (P=0.4607 and P=0.9440, respectively). However, the alloimmunized group had more RBC transfusion episodes than the non-alloimmunized group (17.5 [10.0～26.0] vs. 7.0 [6.0～9.0]; P=0.0016). Also, the RBC transfusion volume was higher in the alloimmunized group (37.1 units [20.5～48.3] vs. 14.0 units [12.6～16.6]; P=0.0020). The number of PLT transfusion episodes and the PLT transfusion volume also varied significantly between the two groups (P=0.0269, P=0.0249, respectively). However, the number of FFP transfusion episodes and the FFP transfusion volumes were not significantly different (P=0.1328 and P=0.1704, respectively).

The alloimmunized group's characteristics were analyzed (Table 2). A total of 18 out of 571 patients developed alloantibodies. Twenty-two alloantibodies were identified, but seven patients had unidentified

Table 2. Alloantibodies detected in patients with hematologic diseases

No.	Age	Sex	Ab.	Dis.	Period between Ab detection and last transfusion	RBC episodes	RBC volume (unit)
1	60	F	E	LYM	1213 days	26	47.6
2	58	F	E	MM	259 days	6	9.6
3	54	M	Jk(a)	CMML	5 days	17	42
4	69	M	E	MDS	26 days	70	128.8
5	74	M	E, c, Le(a)	MDS	8 days	15	21.6
6	49	F	unid	CML	18 days	5	9.4
7	72	F	C, Jk(a), Le(a)	LYM	5 days	18	32.2
8	71	M	unid	ET	9 days	7	8.8
9	57	M	unid	LYM	232 days	24	46.8
10	41	F	E	MDS	30 days	41	91
11	49	M	E	APL	209 days	10	19.8
12	58	F	E, unid	APL	640 days	26	48.8
13	73	M	C, Kp(a)	MDS	5 days	59	112.6
14	71	M	C, e	MDS	84 days	91	128
15	65	F	E, unid	ITP	2121 days	8	22.4
16	46	F	E, unid	AML	159 days	10	16
17	63	M	E	AA	7 days	12	25
18	71	F	E, c, unid	AA	45 days	23	43

1 unit is 400 mL of RBCs, FFP, PLTs.

Abbreviations: Ab, alloantibodies; Dis, disease; Episodes, the number of RBC transfusion episodes; Volume, RBC transfusion volume; LYM, lymphoma; Unid, unidentified antibodies; ET, essential thrombocythemia; APL, acute promyelocytic leukemia.

antibodies. Seven patients formed only one alloantibody, while 11 patients formed more than two alloantibodies. Antibodies belonging to the Rh group were the most frequently identified (17 of 22 alloantibodies), among which the anti-E antibodies were most common (11 of 17 Rh alloantibodies). Apart from that, anti-C (3 cases), anti-c (2 cases), anti-e (1 case), anti-Jk(a) (2 cases), anti-Kp(a) (1 case) and anti-Le(a) (2 cases) antibodies were also recognized.

The alloimmunization rates varied according to the disease group (Table 3). AA and MDS/CMML patients showed a high alloimmunization rate. The alloimmunization rate among AA patients was 6.25%. The difference in alloimmunization rate with the other disease groups was not statistically significant (P=0.2671). The alloimmunization rate of MDS/MML patients at 7.69%, was significantly different from that of the other groups (P=0.0256). There were also significant differences in the amount of RBC transfusions received between the disease groups (Fig. 2). The MDS/CMML patients received significantly more RBC transfusions than the other groups. In the multiple logistic regression analysis comparing the number of RBC transfusions between the disease groups, the odds ratio (95% CI) in MDS/CMML patients was 2.5112 (0.8740～7.2153). The AA, AML, and ALL patients also received several RBC transfusions, but the rate of alloimmunization was not significantly different in these patients.

In the non-alloimmunized group, the patients were further divided into two groups according to the transfusion volume, viz. the massive transfusion group, and the non-massive transfusion group. The massive transfusion group included patients who had received more than 25 units of RBCs. After including the alloimmunized group, the age and sex of the subjects in the three groups were compared. The results are summarized in Table 4. The age of

Table 3. Differences in alloimmunization between disease groups

Disease type	Total Patients (N=571)	Alloimmunization		*P*-value
		No (N=553)	Yes (N=18)	
AA, N (%)	32	30 (93.7)	2 (6.3)	0.2671
AML, N (%)	108	105 (97.2)	3 (2.8)	1.0000
ALL, N (%)	40	40 (100.0)	0 (0.0)	0.6288
MPN, N (%)	57	55 (96.5)	2 (3.5)	0.6984
MDS/CMML, N (%)	78	72 (92.3)	6 (7.7)	0.0256
Lymphoma/CLL, N (%)	109	107 (98.2)	2 (1.8)	0.5473
MM/MGUS/PCL, N (%)	77	75 (97.4)	2 (2.6)	1.0000
ITP, N (%)	47	46 (97.9)	1 (2.1)	1.0000
Others, N (%)	23	23 (100.0)	0 (0.0)	

Abbreviations: AA, aplastic anemia; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MPN, myeloproliferative neoplasm; MDS, myelodysplastic syndrome; CMML, chronic myelomonocytic leukemia; CLL, lymphoma and chronic lymphocytic leukemia; MM, multiple myeloma; MGUS, monoclonal gammopathy of undetermined significance; PCL, plasma cell leukemia; ITP, idiopathic thrombocytopenic purpura.

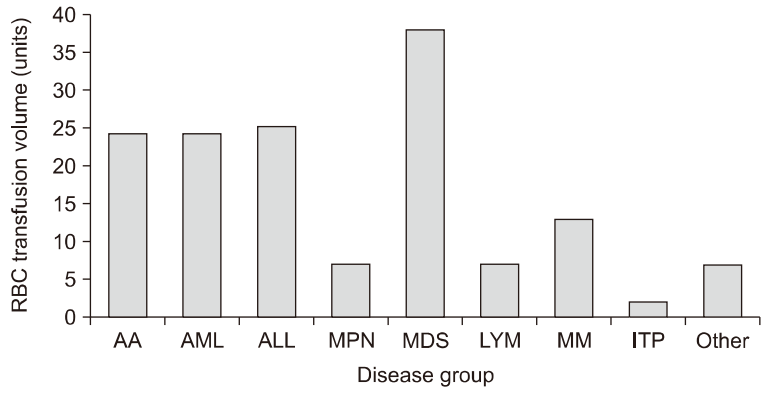

Fig. 2. RBC transfusion volumes by disease type (1 unit is 400 mL RBCs, FFP, PLTs).

Table 4. Characteristics of patients who received more than 25 units of RBCs.

Variables	Alloimmunized group (N=18)	Non-alloimmunized group		*P*-value
		No-massive transfusion (N=363)	Massive transfusion (N=190)	
Age (years), Median (95% CI)	61.5 (55.2～71.0)	63.0 (61.0～65.0)	56.0 (53.0～59.0)	0.0035
Male, N (%)	50.0	53.7	53.7	0.9530

the massive transfusion group was significantly lower than that of the other groups (*P*=0.0035). The male-to-female ratio was similar in all groups (*P*=0.9530).

Discussion

The risk of RBC alloimmunization is affected by various factors, such as the relative frequency of each antigen in the population, antigenicity, and the frequency and timing of the RBC antigen exposure [14-16]. In several international studies, it has been shown that the alloimmunization rate in transfused patients was about 1～7% [3,4]. However, in Korean studies, the alloimmunization rate has been reported to be 0.3～1.73% [13,17-19]. Given that these rates are comparatively low, it can be inferred that the importance of alloantibodies is often not well known to medical staff in Korea. In this study, patients with hematologic diseases showed a higher rate of incidence of alloimmunization.

In previous studies, one unit of RBC transfusion elevated the risk of alloimmunization by 1% [20]. The incidence of alloimmunization increased with the RBC transfusion volume and number of RBC transfusions. Consistent with these results, the alloimmunized group in this study had received more RBC transfusions. However, the volume of RBC transfusions given until antibody detection was not high at about 14.0 units of RBCs, which was similar to the volume of RBC transfusions given in the non-alloimmunized group. These results suggest that not only the frequency and volume of RBC transfusions but also various other factors may affect the occurrence of alloimmunization. Like RBC trans-

fusions, the frequency and volume of non-matched PLT transfusions were important risk factors for the development of alloimmunization [21]. In this study, the alloimmunized group had more PLT transfusions, and hence repeated PLT transfusions may also cause alloimmunization.

In Korea, the Kell group antibodies are rarely detected [13]. In this study, Rh group antibodies were the most commonly identified (58.6%), and among them, anti-E antibodies were the most prevalent (64.7% of all Rh antibodies). Because the proportion of alloantibody types varies by race and country [1], extended RBC matching in Korea should be considered according to the alloantibodies specific to Korea. Thus, the Kell group antigen matching will not be cost-effective in Korea.

Some studies have reported that factors such as age and sex were associated with the incidence of alloimmunization [6,14]. The Dutch transfusion guidelines recommend that women younger than 45 years old should receive cEK-compatible RBCs to prevent hemolytic disease in their newborns [11]. However, in this study, age and sex were not significantly different between the two groups. These discrepancies between the studies may be due to differences in race, study methods, or investigated groups. Also, in this study, non-alloimmunized patients who had received massive transfusions were younger than the patients in the other groups. Although this was not a prospective study, the results suggest that age may be related to alloimmunization. Gender was not associated with alloimmunization in this study. However, further studies using a larger patient population may be needed.

In the alloimmunized group, 8 of the 18 patients did not have detectable alloantibodies in their follow-up samples. These patients are more likely to receive repeated blood transfusions, and therefore require special attention prior to transfusions. Especially, if the patients receive blood transfusions in different hospitals, a hemolytic reaction may occur due to the presence of previous alloantibodies. To prevent this eventuality, extended RBC matching from the first transfusion itself is warranted to reduce acute and delayed hemolytic reactions even after long-term repeated transfusions.

This study provides valuable information on alloimmunization rates specific to the Korean population. In this study, the alloimmunization rate in patients with hematologic diseases was higher than that of general patients. Also, both the number of RBC transfusions and the RBC transfusion volumes were associated with a higher incidence of alloimmunization. Likewise, the frequency and volume of PLT transfusions were also associated with alloimmunization. In Korea, the Rh group antibodies are the most prevalent, and extended antigen matching for the Rh blood group is preferentially needed. Younger patients, even those who received a massive RBC transfusion, showed a low incidence of alloimmunization. Therefore, age may also be a factor affecting the occurrence of alloimmunization. Therefore, extended RBC matching is considered necessary in elderly hematologic disease patients.

Some limitations of this study are as follows: First, this was a retrospective study and hence the relevance of the factors associated with alloimmunization has not been clearly demonstrated. Also, there were only 18 subjects in the alloimmunized group. In the comparison between disease groups, there

were only 0～6 alloimmunized patients in each group. Therefore, further prospective studies with larger sample sizes will be needed to clarify the relationships between alloimmunization and various factors.

In conclusion, extended RBC matching for the Rh subgroup may help to reduce the alloimmunization risk in patients with hematologic diseases. In addition, patients who expect to receive repeated transfusions will benefit from extended RBC matching. Age and the type of the disease are important risk factors for alloimmunization. Some unexpected findings in this study should be further evaluated and considered for a cost-effective analysis. Further studies involving larger patient populations should be performed to evaluate in detail the various factors associated with the development of alloimmunization.

요 약

배경: 혈액질환이 있는 환자들은 적혈구나, 혈소판, 신선동결혈장 등의 혈액제제를 반복적으로 수혈 받는 경우가 많다. 이러한 환자들은 반복적인 적혈구 항원에 대한 노출로 적혈구 동종면역이 발생할 가능성이 높다. 본 연구에서는 반복 수혈이 실시된 혈액질환 환자를 대상으로 extended RBC matching의 필요성을 연구해 보고자 하였다.

방법: 2008년 1월부터 2012년 12월까지 동아대학교병원에서 골수검사를 시행한 환자를 대상으로 하였다. 총 571명을 대상으로 연구를 시행하였다. 각 환자의 진단명, 동정된 비예기항체, 농축적혈구, 혈소판, 신선동결혈장의 수혈횟수와 양을 후향적으로 조사하였다.

결과: 동종면역 발생율은 3.15%였다. 동정된 비예기항체중 Rh 군의 항체가 58.6%로 가장 많았다. 비예기항체 발생군이 미발생군에 비해 적혈구 수혈 횟수가 더 많았고(P=0.0016), 수혈양도 의미 있게 많았다(P=0.0020). 또한 혈소판 수혈 횟수와 양도 비예기항체 발생군에서 의미있게 많았다. 성별이나 나이, 신선동결혈장 수혈에 대해서는 두 군 간에 통계적으로 유의한 차이를 보이지 않았다.

결론: 적혈구 수혈 횟수 및 양이 많을수록 비예기항체가 생길 가능성이 높은 것을 알 수 있었다. 또한 혈소판 수혈 횟수 및 양도 많을수록 비예기항체가 생길 가능성에 영향을 미쳤다. 반복수혈이 예상되는 고령의 혈액질환 환자군에서 일차적으로 Rh 항원이 적합한 혈액을 수혈하는 것이 필요할 것으로 생각되었다.

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