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Red blood cell alloimmunization and other transfusion-related complications in patients with transfusion-dependent thalassemia: a multi-center study in Thailand

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Abstract

Background: Thalassemia is a common genetic disease in Southeast Asia. Red blood cell (RBC) transfusion is an essential treatment for severe forms of thalassemia. We performed a study to demonstrate RBC alloimmunization and other transfusion-related complications in patients with transfusion-dependent thalassemia (TDT).

Study design and methods: A multi-center web-based registry of TDT was conducted in eight medical centers across Thailand. Thalassemia information, transfusion therapy, and transfusion-related complications were collected. Factors associated with each complication were demonstrated using the logistic regression analysis.

Results: One-thousand patients, 449 males (44.9%), were enrolled in the study. The mean age was 23.9±15.4 years. The majority of patients, 738 (73.8%) had hemoglobin E/beta-thalassemia. Four hundred and twenty-one transfusion-related complications were reported from 357 patients (35.7%). Alloimmunization was the most common complication which was found in 156 patients (15.6%) with 284 positive antibody tests. The most frequent antibodies against RBC were anti-E (80/284, 28.2%) followed by anti-Mi^a (45/284, 15.8%) and anti-c (32/284, 11.3%). Age ≥ 3 years at initial blood transfusion, splenomegaly, higher frequencies and volumes of transfusion were significant factors associated with alloimmunization. None of the patients had to terminate blood transfusion due to multiple alloantibodies. Other commonly seen complications were allergic reactions (130, 13.0%), autoimmune hemolytic anemia (70, 7.0%) and febrile non-hemolytic transfusion reaction (54, 5.4%).

Conclusions: Transfusion-related complications, especially alloimmunization, were common among Thai patients with TDT. Extended RBC antigen-matching for the Rh system and Mi^a should be implemented to prevent the development of alloantibodies in multi-transfused patients.

Keywords

alloimmunization; complications; risk factors; TDT; thalassemia; transfusion practice

Introduction

Thalassemia disease is one of the most frequent inherited red blood cell (RBC) disorders worldwide.[1] The prevalence of thalassemia is high among the population in Africa, the Middle East, Mediterranean regions, South Asia, and Southeast Asia.[2] Hemoglobin E (Hb E)/beta-thalassemia is a common type of beta-thalassemia found in Southeast Asia,

particularly in Thailand, where Hb E is the most frequent hemoglobin variant.[3,4] There is a wide spectrum of clinical severity of the Hb E/beta-thalassemia, which varies from mild to moderate, non-transfusion-dependent thalassemia (TDT) to severe and transfusion-dependent thalassemia (TDT). These clinical diversities among the patients may be explained by several genetic modifiers, including coinheritance with alpha-thalassemia, high hemoglobin F (Hb F) synthesis, and polymorphisms in some quantitative trait loci (e.g., *Xmn1-HBG2*, *BCL11A*, and *HMIP*).[5–7]

Advances in the knowledge of the pathogenesis of thalassemia have led to novel therapeutic approaches, including improving ineffective erythropoiesis, modulating iron metabolism, and gene therapy.[8,9] However, chronic RBC transfusion remains the essential treatment modality in patients with TDT.

Alloimmunization is a challenging problem among individuals with chronic transfusion. It has been reported from 11.4% to 42.5% in patients with thalassemia with different types of alloantibodies based on the ethnic groups.[10–16] Antibodies against the Rh and Kell groups are the most frequent alloantibodies in patients with thalassemia.[17] Transfusions with extended matching for RBC antigen blood can minimize the risk of alloimmunization.[18,19] Previous studies demonstrate several contributing factors for developing alloimmunization in patients with thalassemia, including the age at initial transfusion, gender, splenectomy, frequency of transfusion, treatment duration, the number of units transfused, and mismatch between donor-recipient ethnic background.[10,13–15]

A standard treatment guideline for blood transfusion has been established in patients with TDT, the information is mostly based on beta-thalassemia major.[20] In Thailand, thalassemia is one of the significant public health problems and Hb E/beta-thalassemia is predominant. We, therefore, performed a multi-center study to demonstrate the transfusion-related complications in a large group of patients with TDT from all regions of Thailand.

Methods

This is a result of a web-based thalassemia registry in Thailand. The registry is operated by the Red Blood Cell Disorders and Aplastic Anemia Committee, under the support of the Thai Society of Hematology (TSH). Eight university hospitals including 1) Srinagarind Hospital, Khon Kaen, 2) Chiang Mai University Hospital, Chiang Mai, 3) Ramathibodi Hospital, Bangkok, 4) Siriraj Hospital, Bangkok, 5) Chulalongkorn Hospital, Bangkok, 6) Songklanagarind Hospital, Songkla, 7) Phramongkutklao Hospital, Bangkok, and 8) Thammasat Hospital, Pathumtani enrolled the patients and contributed the data. Eligible participants were patients diagnosed with TDT who were regularly followed and received regular RBC transfusions < 8 weeks intervals at the enrolling centers. The transfusion criteria were based on the Thalassaemia International Federation (TIF) guideline for TDT.[20] The diagnosis of thalassemia disease was confirmed by Hb typing, by either high-performance liquid chromatography or capillary electrophoresis techniques, or DNA analysis.

The registration period started from January 2021 to December 2021. Study data were collected and managed using Research Electronic Data Capture (REDCap)[21], an electronic data capture tool hosted by Khon Kaen University. The study aimed to determine the transfusion-related complications in Thai patients with TDT.

Thalassemia information:

The medical histories of thalassemia and RBC transfusion were collected as follows; age at the first diagnosis, age at the first transfusion, history of splenectomy, frequency of RBC transfusion, volume of transfusion, type of RBC products, and transfusion-related complications.

Laboratory investigations:

Laboratory tests were collected as follows; the mean pre-transfusion Hb level in the previous six months and the mean serum ferritin level in the last year, the presence of antibodies, and the type of alloantibodies and autoantibody.

Statistical analysis

All statistical analysis was performed using the STATA program version 10 (StataCorp, College Station, TX). Categorical variables were reported as frequency and percentage. Continuous variables were presented as mean ± standard deviation (SD). Logistic regression analysis was used to identify factors associated with alloantibodies. A p-value <0.05 was considered statistically significant.

Results

One-thousand patients, 449 males (44.9%), were recruited for the study. The majority of the patients had severe forms of thalassemia, including 738 patients with HbE/beta-thalassemia (73.8%) and 113 patients with beta-thalassemia major (11.3%). The mean age in this cohort was 23.9±15.4 years. Splenectomy was performed in 264 patients (26.4%). (Table 1)

Red blood cell transfusions

More than half of the patients received a regular RBC transfusion every four weeks (598 patients, 59.8%). The most common volume of RBC transfusion was two units of RBC products (566 patients, 56.6%). Leukocyte-depleted RBCs (pre-storage filtered) were the most common RBC products transfused in these patients, followed by leukocyte-poor RBCs. (Table 2)

Transfusion-related complications

Four-hundred and twenty-one transfusion-related complications were reported in 357 patients (35.7%). Alloimmunization was the most common transfusion complication in this cohort, which was found in 156 patients (15.6%). None of the patients had to terminate blood transfusion due to multiple alloantibodies. Allergic reactions (rash, angioedema) were the second most frequent transfusion-related complication that occurred in 130 patients (13%). (Table 2) The other complications were autoimmune hemolytic anemia (70

patients, 7.0%), febrile non-hemolytic transfusion reaction (54 patients, 5.4%), anaphylaxis, transfusion-related infection and transfusion-related acute lung injury.

Alloantibodies against red blood cell

A total of 284 positive alloantibodies was found in 156 patients. Of those with alloantibodies, 82 patients had one antibody (52.6%), 41 patients had two antibodies (26.3%), 14 patients had three antibodies (8.9%), and 19 patients had more than three antibodies (12.2%). Nearly half of those patients with alloimmunization had multiple antibodies against RBC (74 patients, 47.4%). Anti-E was the most common antibody found in 80 patients from 156 patients (80, 51.3%). While anti-Mi^a is the second most common (45, 28.8%), and anti-c the third most common (32, 20.5%) alloantibodies found in this cohort. (Table 3)

Factors associated with the development of alloantibodies

Of 156 patients with alloimmunization, 41 patients underwent splenectomy and the remaining 115 patients had intact spleen (26.3% vs. 73.7%, p-value =0.9). Multivariate analysis revealed factors associated with alloimmunization as follows; 1) age at initial transfusion ≥ 3 years (adjusted odds ratio [AOR]= 2.0, 95% confidence interval[CI] 1.3–3.0, p-value 0.002), 2) enlargement of the spleen below the costal margin per 1-cm increase (AOR=1.1, 95%CI 1.04–1.16, p-value <0.005), 3) transfusion interval ≤ 4 weeks (AOR=2.4, 95%CI 1.1–5.2, p-value 0.03), and 4) volume of RBC transfusion > 15 mL/kg (AOR=5.5, 95%CI 1.3–23.4, p-value 0.02). (Table 4)

Factors associated with the development of autoantibodies

Of 70 patients with autoantibodies, 20 patients had alloimmunization, and 50 patients did not have alloantibodies (28.6% vs. 71.4%, p-value = 0.002). Multivariate analysis revealed significant risk factors for autoimmunization as follows; 1) presence of alloimmunization (AOR= 3.5, 95% CI 1.8–7.0, p-value <0.005) and 2) enlargement of the spleen below the costal margin per 1-cm increase (AOR=1.1, 95%CI 1.01–1.15, p-value 0.02). (Table 5)

Factors associated with the development of allergic transfusion reactions

Multivariate analysis revealed factors significantly associated with allergic reactions as follows; 1) age per 1 year increase (AOR = 0.9, 95% CI 0.8–0.9, p-value <0.005), 2) transfusion interval ≤ 4 weeks (AOR = 4.7, 95%CI 1.1–20.2, p-value 0.03), and 3) pre-transfused hemoglobin per 1 g/dL increase (AOR = 1.3, 95%CI 1.1–1.5, p-value 0.001). (Table 6)

Discussion

We demonstrate transfusion practices and transfusion-related complications in Thai patients with TDT. Alloimmunization remains one of the major problems among these patients who receive regular RBC transfusions. The prevalence of alloimmunization against RBC is 15.6% in this study, which is comparable to the previous studies in patients with TDT.[17] Of the 284 positive tests, antibodies against the Rh system are the most common antibodies found, particularly against the E antigen (28.2%) and c antigen (11.3%), which

encompass nearly 40% of total antibodies. These findings are consistent with the literature that antibodies against the Rh system are the most frequent alloantibody found in patients with TDT.[17] The second most common antibody in this study is anti-Mi^a which is different from the studies in the Middle Eastern and Western countries, where antibodies against the Kell system are the second most common alloantibodies.[14,15,17] However, these findings are similar to the previous studies in Thailand, Singapore and Hong Kong, which may be explained by the similarity in the Asian background population.[11,16,22] Moreover, a study of antigen frequencies of Rh (C, c, E, e) and MNS (M, Mi^a) blood group systems among Thai blood donors showed low frequencies of E (32.2%), c (34.4%), and Mi^a (17.9%) antigen.[23] These data support the high incidence of alloimmunization against E antigen (28.2%), c antigen (11.3%), and Mi^a antigen (15.8%) in this cohort, which may be explained by the mismatch between donor and recipient antigen. In Thailand, the national blood bank policy and the practice guideline by the Thai Society of Hematology recommend extended RBC matching, including the Rh system (C, c, E, e) and Mi^a in multi-transfused patients.[24] Extended RBC matching, however, is not a standard transfusion practice in general transfusion centers. These findings highlighted the need for national registration of alloimmunization database in regularly transfused patients and implementation of RBC antigen-matching, including the Rh system and Mi^a, in the general transfusion centers for patients with TDT.

Age at the first transfusion is one of the well-known significant factors in the development of alloimmunization. The previous studies found that age at initial transfusion younger than 1–3 years old significantly decreased the risk of alloimmunization. The mechanism is that early immune stimulation by transfusion at an early age may reduce the risk of alloantibodies due to immune tolerance in these patients.[18,25] Like others, this study found that starting the first transfusion after three years old significantly increased the risk of alloimmunization (AOR = 2.0, p-value 0.002).

Splenectomy is established as a risk factor for the development of alloantibodies in previous studies.[10,14,15,26] In this study, splenectomy did not demonstrate a significant association with alloimmunization. The reason is likely that splenectomy has been declining in the past decades. The number of patients who underwent splenectomy in this cohort is small. An interesting finding is that enlargement of the spleen by physical examination is a significant risk factor for alloimmunization. These patients with splenomegaly may have been a representative of the patients who underwent splenectomy in previous studies. This study demonstrated that an increase in spleen size (per 1 cm) below the costal margin was significantly associated with the development of alloantibodies (AOR = 1.1, p-value < 0.005). These results may be related to the higher requirement of RBC transfusion in patients with splenomegaly than in those without splenomegaly. Therefore, splenic enlargement may have an impact on transfusion requirements.

Higher blood transfusion frequency is one of the risk factors for developing alloimmunization. It may be due to the higher rate of exposure to RBC antigens. In this study, the transfusion interval ≤ four weeks was a significant risk factor for the development of alloantibodies (AOR = 2.4, p-value 0.03). This finding is consistent with the previous study in patients with TDT.[26] This result, however, is different from the previous study in

patients with NTDT, which found that lower blood transfusion frequency was associated with an increased risk of alloimmunization.[16]

The volume of transfusion is demonstrated as contributing factor for alloimmunization in patients who require chronic transfusion, e.g., sickle cell anemia[27,28] and thalassemia[14,29,30]. This study showed that the volume of transfusion > 15 mL/kg of RBC products strongly increased the risk of alloantibodies (AOR = 5.5, p-value 0.02). This finding agrees with previous studies that the cumulative number of units transfused was a predictive factor for alloimmunization in those with TDT.[29,30]

RBC autoantibodies were found in 70 patients (7%). This study showed that the presence of alloimmunization was a significant risk factor for developing autoantibodies (AOR = 3.5, p-value <0.005), which is similar to the previous reports in patients with thalassemia.[16,31] Splenectomy was an independent risk factor for autoantibodies in some studies.[10,31] While, this cohort demonstrated that splenomegaly was significantly associated with autoantibodies (AOR = 1.1, p-value 0.02). As mentioned earlier, patients with splenomegaly may represent those who underwent splenectomy in the past. The mechanisms of the association between autoimmunization and alloimmunization remained unclear. However, the proposed mechanism is that the presence of alloantibodies from previous transfusion leads to the changes in the antigenic epitopes on red blood cells, which promote the production of autoantibodies.[32]

Allergic reactions were the second most common transfusion-related complications in this cohort. Previous studies demonstrated that allergic reactions were more prevalent among young patients[33–35], particularly those with a history of allergies (e.g., food allergies, asthma, allergic rhinitis, pollinosis, or atopic dermatitis).[35] Like others, this study found that advanced age was associated with a reduced risk of allergic reactions (AOR = 0.9, p-value < 0.005). Moreover, frequent transfusion (≤ four weeks) is a significant risk factor for developing allergic transfusion reactions (AOR = 4.7, p-value 0.03), which may be due to high exposure to allergens. An interesting finding was that higher pre-transfused hemoglobin was associated with an increased risk of allergic reactions (AOR = 1.3, p-value 0.001).

The limitation of this study was a nature of cross-sectional study design. Therefore, we could not demonstrate the incidence and the cause-effect relationship of the risk factors and the outcomes. Also, information on the persistence of alloantibodies was not available.

In conclusion, transfusion-related complications, especially alloimmunization, were common and remained a challenging problem among Thai patients with TDT. Alloantibodies against the Rh system and anti-Mi^a were the most frequently detected antibodies. Initial transfusion after three years old, splenomegaly, the large volume of transfusion, and higher transfusion frequency were significant risk factors for developing alloimmunization. Extended RBC antigen-matching to include the Rh system and Mi^a should be implemented for Thai patients with TDT. The recommendation can be adapted for patients from Southeast Asia who have similar genetic background.

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Table 1

Baseline data for study participants

Characteristics	Patients (n=1,000)
Mean age ± SD, years	23.9±15.4
Mean age at initial blood transfusion ± SD, years	
All subjects	5.9±10.8
Hb E/beta-thalassemia	5.8±10.0
Beta-thalassemia major	2.4±4.6
Other	9.1±15.6
Mean pre-transfused Hb ±SD, g/dL	8.1±1.4
Mean serum ferritin ± SD, ng/mL	2,161±2,179
Gender, n (%)	
Female	551 (55.1)
Male	449 (44.9)
Splenectomy, n (%)	
No	736 (73.6)
Yes	264 (26.4)
Current iron chelation, n (%)	
None	62 (6.2)
Deferoxamine monotherapy	12 (1.2)
Deferiprone monotherapy	485 (48.5)
Deferasirox monotherapy	237 (23.7)
Combined Deferoxamine + Deferiprone	78 (7.8)
Combined Deferoxamine + Deferasirox	55 (5.5)
Combined Deferiprone + Deferasirox	71 (7.1)
Phenotype group, n (%)	
Hb E/beta-thalassemia	738 (73.8)
Beta-thalassemia major	113 (11.3)
Hb H disease with Hb CS	65 (6.5)
EABart's disease†	23 (2.3)
EABart's disease with HbCS‡	44 (4.4)
EFBart's disease§	3 (0.3)
EFBart's disease with HbCS¶	3 (0.3)
Other	11 (1.1)

Abbreviation: Hb, hemoglobin; Hb CS, hemoglobin Constant Spring.

†Compound heterozygous Hb H and heterozygous Hb E.

‡Compound heterozygous Hb H with Hb CS and heterozygous Hb E.

§Compound heterozygous Hb H and homozygous Hb E.

¶Compound heterozygous Hb H with Hb CS and homozygous Hb E.

Table 2

Red blood cell transfusion in 1,000 patients with thalassemia

Characteristics	Patients (n=1,000)
Frequency of transfusion, n (%)	
1 week	1 (0.1)
2 weeks	12 (1.2)
3 weeks	122 (12.2)
4 weeks	598 (59.8)
5 weeks	23 (23.0)
6 weeks	112 (11.3)
8 weeks	127 (12.8)
Other	5 (0.5)
Volume of RBCs per transfusion, n (%)	
1 unit	158 (15.8)
2 units	566 (56.6)
5–10 mL/kg	14 (1.4)
10–12 mL/kg	63 (6.3)
12–15 mL/kg	176 (17.6)
> 15 mL/kg	9 (0.9)
Other	14 (1.4)
Type of red blood cell products *, n (%)	
Red Blood Cells (RBCs)	33 (3.3)
Leukocyte-poor RBCs	548 (54.8)
Leukocyte-depleted RBCs	625 (62.5)
Single-donor RBCs	2 (0.2)
Transfusion-related adverse events **, n (%)	
None	643 (64.3)
Anaphylaxis	6 (0.6)
Febrile non-hemolytic transfusion reaction (FNHTR)	54 (5.4)
Alloantibody	156 (15.6)
Allergic reactions	130(13.0)
Autoimmune hemolytic anemia	70 (7.0)
Transfusion-related infection	4 (0.4)
Transfusion-related acute lung injury (TRALI)	1 (0.1)

* some patients received multiple types of RBC products

** some patients have multiple adverse events

Table 3

Type of 284 positive alloantibodies tests in 156 patients.

Type of antibodies	Frequency of positive tests (n =284) n, (%)	Frequency of patients (n = 156) n, (%)
Rh system		
Anti-E	80 (28.2)	80 (51.3)
Anti-e	3 (1.1)	3 (1.9)
Anti-C	8(2.8)	8 (5.1)
Anti-c	32 (11.3)	32 (20.5)
MNS system		
Anti-Mi[a]	45 (15.8)	45 (28.8)
Anti-M	1 (0.3)	1 (0.6)
Anti-N	1 (0.3)	1 (0.6)
Anti-S	8 (2.8)	8 (5.1)
Kidd system		
Anti-Jk[a]	8 (2.8)	8 (5.1)
Anti-Jk[b]	4 (1.4)	4 (2.6)
Duffy system		
Anti-Fy[a]	0	0
Anti-Fy[b]	5 (1.8)	5 (3.2)
Lewis system		
Anti-Le[a]	17 (6.0)	17 (10.9)
Anti-Le[b]	6 (2.1)	6 (3.8)
Diego system		
Anti-Di[a]	11 (3.9)	11 (7)
PP_1P^k system		
Anti-P_1	6 (2.1)	6 (3.8)
Unidentified	49 (17.3)	49 (31.4)

*some patients have multiple alloantibodies

Table 4

Multivariate analysis of factors associated with alloimmunization

Variables	AOR	95% CI	p-value
Enlargement of the spleen below the costal margin (per 1 cm increase)	1.1	1.04–1.16	<0.005
Age at initial blood transfusion ≥ 3 years	2.0	1.3–3.0	0.002
Pre-transfusion hemoglobin (per 1 g/dL increase)	0.9	0.8–1.1	0.6
Beta-thalassemia	1.0	0.6–1.8	0.8
Blood transfusion interval ≤ 4 weeks	2.4	1.1–5.2	0.03
Volume of RBC transfusion > 15 mL/kg	5.5	1.3–23.4	0.02

Abbreviation: AOR= adjusted odds ratio, 95% CI= 95% confidence interval

Table 5

Multivariate analysis of factors associated with autoimmunization

Variables	AOR	95% CI	p-value
Enlargement of the spleen below the costal margin (per 1 cm increase)	1.1	1.01–1.15	0.02
Presence of prior alloimmunization	3.5	1.8–7.0	<0.005
Beta-thalassemia	0.8	0.4–1.9	0.6
Blood transfusion interval ≤ 4 weeks	1.2	0.4–3.8	0.6
Age at initial blood transfusion ≥ 3 years	0.9	0.5–1.7	0.7

Abbreviation: AOR= adjusted odds ratio, 95% CI= 95% confidence interval

Table 6

Multivariate analysis of factors associated with allergic transfusion reactions

Variables	AOR	95% CI	p-value
Enlargement of the spleen below the costal margin (per 1 cm increase)	1.01	0.9–1.1	0.6
Age (per 1 year increase)	0.9	0.8–0.9	<0.005
Blood transfusion interval ≤ 4 weeks	4.7	1.1–20.2	0.03
Pre-transfusion hemoglobin (per 1 g/dL increase)	1.3	1.1–1.5	0.001
Beta-thalassemia	1.2	0.7–2.1	0.4

Abbreviation: AOR= adjusted odds ratio, 95% CI= 95% confidence interval