IJSCIA

International Journal of Scientific Advances
ISSN: 2708-7972
Volume: 4 | Issue: 1 | Jan – Feb 2023 Available Online: www.ijscia.com
DOI: 10.51542/ijscia.v4i1.18

The Correlation Between Frequency of Transfusion and Alloimmunization in Transfusion-Dependent Thalassemia Patients

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ABSTRACT

Thalassemia is a red blood cell disorder caused by impaired synthesis of hemoglobin and is genetically inherited. Based on the need for transfusion, thalassemia is divided into transfusion-dependent thalassemia and non-transfusion-dependent thalassemia. Transfusion-dependent thalassemia patients require life-long red blood transfusions. Transfusions that are carried out will cause complications reactions to the body such as immune reactions, i.e. Alloimmunization. Alloimmunization remains a major problem in transfusion dependent thalassemia patients. Aims to determine the relationship between the frequency of transfusions and the incidence of alloimmunization in transfusion-dependent thalassemia patients. This research is an observational analytic study with a retrospective approach using secondary data in the form of medical records at the Pediatric Hematology Oncology Installation, Blood Transfusion Installation, and Central Medical Records at RSUD Dr. Soetomo 2019–2020. This study used 193 research samples, 165 patients (85.5%) did not experience alloimmunization and alloimmunization was found in 28 patients (14.5%). In the female group, 21 of 99 (21.2%) patients and in the male group 7 of 94 (7.4%) patients who had alloimmunization. The distribution of transfusion-dependent thalassemia patients get a transfusion frequency of 1–10 times (35.7%) before had alloimmunization. The relationship between the frequency of transfusions and the incidence of alloimmunization has p value = 0.65 (>0.05). There is no significant correlation between the frequency of transfusions and the incidence of alloimmunization in transfusion-dependent thalassemia patients.

Keywords: alloimmunization; thalassemia; transfusion

INTRODUCTION

Thalassemia is a hereditary blood disorder that is characterized by impaired synthesis of the hemoglobin chain. According to data from the Ministry of Health 2019, in Indonesia there are more than 10,531 thalassemia patients and it is estimated that every year the number of babies born with thalassemia is 2,500 babies.[1] Epidemiological research in Indonesia proves that the number of beta thalassemia genes in Indonesia ranges from 3-10%. This shows that the incidence of thalassemia in Indonesia is quite a lot. Classification of thalassemia based on clinical severity and need for transfusion is divided into 2, Transfusion-Dependent Thalassemia (TDT) and Non-Transfusion-Dependent Thalassemia (NTDT).[2] Transfusion-dependent thalassemia requires regular blood transfusions for life as main therapy. Transfusions continuously can make complications or risks, such as an alloimmunization. Alloimmunization is transfusion reaction which is an immune reaction to exposure to red blood cell antigens originating from other individuals that the body considers foreign.[3] Alloimmunization against red blood cell antigens is an immune response that is usually stimulated by blood products and is one of the complications of red blood cell transfusion.[4] Alloimmunization is a common complication of transfusion therapy and occurs in 10-20% of patients with thalassemia.[2] Rates of thalassemia patients who undergo repeated transfusions experience alloimmunization range from 2.5% to 42% in various regions of the world.[5] Red blood cell alloantibodies in transfusion-dependent thalassemia will cause difficulty in patients to cross-matching and delays in obtaining compatible blood for transfusion.[6]

Research by Romphruk et al., 2019 proved that the frequency of alloimmunization was significantly lower in patients who received less than 20 units of transfused blood compared to patients who received more.[7]

The study of El Kababi et al., 2019 also reported a significant correlation between the transfusion interval and the formation of alloantibodies, that the alloimmunization rate was found to be lower in the group that received transfusions with intervals of more than 3 weeks compared to those who received transfusions with intervals of less than 3 weeks.[8] Research by Zheng and Maitta, 2016 proved that greater exposure to red blood cell units can result in higher red blood cell alloimmunization.[9] The level of production of alloantibodies has a significant correlation with the number of units exposed to blood.[10] The incidence of RBC alloimmunization was higher in patients who were frequently exposed to transfusions and increased when the total was more units of blood have been transfused. Alloimmunization events in patients undergoing routine transfusion therapy such as thalassemia can be prevented by pre-transfusion screening and identification of antibodies prior to transfusion to determine the presence or absence of alloantibodies formed due to previous exposure to red blood cell antigens.[3] The use of blood from antigen-matched donors is effective in reducing the rate of alloimmunization.[2]

METHODS

This is an analytical observational research with a retrospective approach using secondary data in the form of medical records at RSUD Dr. Soetomo 2019 -- 2020. The study population includes pediatric transfusion-dependent thalassemia patients which are under 18 years of age. This study was approved by the Ethics Committee of Dr. Soetomo Surabaya with ethical clearance number 1076/105/4/XI/2021.

A total of 193 transfusion-dependent thalassemia patients who underwent alloimmunization. Were included in this study. We analyzed the relationship between the frequency of transfusions and the incidence of alloimmunization. The operational variables used were transfusion records and laboratory data concerning 193 regularly transfused thalassemic children including age, sex, date of first blood transfusion, and antibody screening. The data obtained was processed and statistical analysis was carried out using the Spearman test. The results were analyzed using SPSS statistical software version 23.0.

RESULT

A total of 193 patients were included in the study with inclusion criteria, 28 patients experienced alloimmunization and 165 patients did not experience alloimmunization. They consist of 7 males (25.0%) and 21 females (75.0%). In the age group of pediatric patients who experienced alloimmunization, the majority of respondents were in the 12–18 years old (14 case, 50%). Based on the distribution of blood groups, it was found that most of the transfusion-dependent pediatric thalassemia patients who experienced alloimmunization (39.29%) or did not experience alloimmunization (44.8%) in this study had blood type O while blood type AB had the lowest number of patients.

The distribution of transfusion frequencies in alloimmunization patients based on all transfusion histories are shown in Table 1. In this study, the frequency of transfusion was the history of transfusion starting from the first's transfusion until the patient first received alloimmunization. There were 10 children (35.7%) experienced alloimmunization after receiving 1–10 transfusions, 11–20 and 41-50 transfusions (3 children, 10,7%), 21–30 and 31–40 transfusions (2 children, 7.1%), in the category of 51–60 transfusions there were no alloimmunization incidence, and >60 transfusions (8 children, 28.6%).

This study shows that the majority of transfusion-dependent pediatric thalassemia patients who experienced alloimmunization received 1-10 transfusions from the initial transfusion until the first time he received alloimmunization. The distribution of the frequency of transfusions in transfusion-dependent pediatric thalassemia patients, starting from the initial transfusion to the first time receiving alloimmunization, which had the largest frequency of 314 transfusions and the smallest, 1 transfusion.

TABLE 1: Distribution of Transfusion Frequencies in Alloimmunization Patients Based on all History of Transfusion.

Total number of transfusion (all history)	N	%
1–10 time(s)	10	35,7%
11–20 times	3	10,7%
21–30 times	2	7,1%
31–40 times	2	7,1%
41–50 times	3	10,7%
51–60 times	0	0,0%
>60 times	8	28,6%
Total patients	**28**	**100%**

The frequency data of transfusions in alloimmunization and non-alloimmunization patients for 2 years (2019–2020) have been shown in Table 2. The total number of transfusions in alloimmunization patients for 2 years had the largest frequency of 122 transfusions and the smallest frequency, 3 transfusions. The distribution of the non-alloimmunization patients had the largest frequency of 85 transfusions and the smallest, 1 transfusion. The correlation between the frequency of transfusions and the incidence of alloimmunization was not statistically significant (P=0.65).

TABLE 2: Distribution of Transfusion Frequency Based on 2 Years (2019–2020) Transfusion History in Alloimmunized and Non-Alloimmunized Patients.

Total number of transfusions	N (%)		*P value*
	Allo-immunization	Non-Allo-immunization	
1–10 time(s)	7 (25,0%)	38 (23,0%)	
11–20 times	5 (17,9%)	30 (18,2%)	
21–30 times	4 (14,3%)	44 (26,7%)	
31–40 times	6 (21,4%)	25 (15,2%)	0,65
41–50 times	3 (10,7%)	17 (10.3%)	
51–60 times	0 (0,0%)	8 (4,8%)	
>60 times	3 (10,7%)	3 (1,8%)	
Total	**28**	**165**	

DISCUSSION

Transfusion-dependent thalassemia patients required repeated regular transfusion. This indicates that the patient will get a lot of exposure to red blood cell antigens. In this study, the frequency of transfusion for 2 years was divided into several categories. Summarizing the difference between alloimmunization and non-alloimmunization patients in relation to the frequency of transfusion in patients who are considered related to the formation of red blood cell alloantibodies. A largest exposure to the red blood cell can cause higher red blood cell alloimmunization.[9] Spearman's test results in this study show that the transfusion frequency relationship with the incidence of alloimmunization in transfusion-dependent thalassemia patients have p value> 0.05 (p = 0.65), there is no significant relationship between the frequency of transfusion and the incidence of alloimmunization in transfusion-dependent thalassemia patients.

The formation of alloantibodies against red blood cell antigens can occur in any repeated transfusions by transfusion-dependent thalassemia patients. As more exposure to different red blood cell antigens can lead to greater production of alloantibodies.[11] Several factors affect due to requirement of blood transfusions, among others, age and gender. According to Kosaryan et al., 2012 there are several causes of alloantibody variations in various countries, such as varying levels of immunogenicity of common blood antigens in a population, the population homogeneity and the percentage of indigenous vs immigrants, and blood transfused sources (from within or outside the region).[12] Every incompatibility in transfused blood units can cause the formation of alloantibodies in patients and complications. Repeated blood transfusion in thalassemia patients can cause alloimmunization which means alloimmunization can reduce the survival of red blood cells and decrease the success of blood transfusion.[13]

Study of Beshlawy 2020 have shown that alloimmunization has a significant relationship with the frequency of transfusions.[14] In line with the study of Davoudi-Kiakalayeh et al., 2017 there is a significant correlation between alloantibody production and the number of exposures to blood units.[6] In addition, other studies have shown a significant relationship regarding the effect of more frequent transfusions on the development of alloimmunization.[15] The occurrence of alloimmunization involves at least 3 contributing elements, such as differences in red blood cell antigens between donor and recipient, recipient's immune status, and immunomodulatory effect of allogeneic blood transfusion on the recipient's immune system.[5] Other factors such as genetics, the population studied, and racial differences between donors and recipients have been shown to affect red blood cell alloimmunization so this can explain why the results of our study differ from several previous studies.[16]

The results of this study indicate that there is no relationship between the frequency of transfusion and the incidence of alloimmunization in transfusion-dependent thalassemia patients. In line with the research of Kosaryan et al. which stated that there was no significant correlation between the presence of alloantibodies with blood transfusion frequencies.[12] The data obtained is one of the determinants in this study and can affect previous research. Data obtained in the history of the patient's transfusion listed in the medical record of Dr. Soetomo might not include transfusion by patients outside the hospital Dr. Soetomo Surabaya so that the history of the transfusion cannot be recorded. Although the data collected is still limited, a previous study showed that there are high cases in individuals who develop blood type antibodies even after a single transfusion.

The higher transfusion requirement is closely related to the presence of IgG that is bounded by red blood cells. Antigen on the surface of red blood cells intrinsically associated with membrane or lipid protein. Clinically, the ability of surface molecules to cause immune responses to be important for transfusion of blood components and tissue and organs transplants.[17] The study states that the possibility of patients experiencing immune responses after blood transfusion is known to vary greatly and many cases are related to several factors such as the clinical condition of the patient and the underlying inflammatory status, the possibility of exposure to foreign antigens, and immunogenicity antigens are visible.[18] There are several analytic factors that affect the detection of alloantibodies and alloimmunization levels such as the performance of antibody screening testing after exposure to transfusion and determination of antibody detection.

Based on our research, the frequency of transfusions has no correlation with the incidence of alloimmunization probably due to the low number of patients. By finding many differences with several previous studies, researchers suspect that the effect of transfusions performed on transfusion-dependent thalassemia patients may be influenced by other factors, such as genetics. Total number of transfusions has no correlation with the incidence of alloimmunization illustrate that the management carried out is good and appropriate. Ideally, thalassemic should be given phenotypically matched blood to reduce the potential for alloantibody formation. As for patients who experience alloimmunization, transfusion management in thalassemia patients can be maximized to minimize red blood cell alloimmunization and autoimmunization among thalassemia sufferers. Pre-transfusion blood grouping and cross-matching is necessary to reduce the possibility of developing alloantibody immunity thereby increasing the efficiency of blood transfusion. In pediatric thalassemia patients, the role of parents is needed regarding parents' awareness and understanding of repeated transfusions and the effects or complications from the therapy they have on children. Parent-child interaction, which includes treatment, promotes successful therapy.[19] Understanding of thalassemia disease can become awareness to increase zero-thalassemia birth.

CONCLUSIONS

Alloimmunization is an important finding in transfusion-dependent thalassemia patients. Several factors might have contributed to this finding, such as the heterogeneity of the population, the difference in the number of studied patients, the differences in age at first transfusion, antigenic differences between the blood donor and the recipient, and the recipient's immune status. Based on the data obtained from the results and discussion, it can be concluded that there is no relationship between the frequency of transfusions and the incidence of alloimmunization in transfusion-dependent thalassemia patients. With the growing of the knowledge and limited data, an extensive multicenter study is needed to assess the frequency of transfusions with alloimmunization events and further prospective studies within a certain time frame to observe the course of thalassemia patients who had alloimmunization.

ACKNOWLEDGMENT

We thank all contributors that participated in writing and compiling this article. The authors report there are no conflicts of interest and we are responsible for the content and writing of the paper. In this study, no funding source was involved in the design or conduct of the research or preparation of the manuscript, and the analyses and opinions expressed are those of the authors alone.

REFERENCES

[1] Kementerian Kesehatan Republik Indonesia. Angka Pembawa Sifat Thalasemia Tergolong Tinggi [Internet]. Kementerian Kesehatan Republik Indonesia. 2019 [cited 2021Jun14]. Available from: https://www.kemkes.go.id/article/view/19052100003/angka-pembawa-sifat-talasemia-tergolong-tinggi.html

[2] Bain B. 2021 guidelines for the management of transfusion dependent thalassaemia (tdt), 4th Edition Cappellini MD, FARMAKISD, PorterJ and Tahera (eds). Thalassaemia International Federation, 2021, ISBN-13 978-9963-717-18-7. British Journal of Haematology. 2023

[3] Maharani EA, Noviar G. Imunohematologi dan Bank Darah. Kementerian Kesehatan Republik Indonesia. 2018;11(3):322.

[4] Dhawan HK, Kumawat V, Marwaha N, Sharma RR, Sachdev S, Bansal D, Marwaha RK, Arora S. Alloimmunization and autoimmunization in transfusion dependent thalassemia major patients: Study on 319 patients. Asian Journal of Transfusion Science. 2014 Jul;8(2):84.

[5] Singer ST, Wu V, Mignacca R, Kuypers FA, Morel P, Vichinsky EP. Alloimmunization and erythrocyte autoimmunization in transfusion-dependent thalassemia patients of predominantly Asian descent. Blood, The Journal of the American Society of Hematology. 2000 Nov 15;96(10):3369-73.

[6] Davoudi-Kiakalayeh A, Mohammadi R, Pourfathollah AA, Siery Z, Davoudi-Kiakalayeh S. Alloimmunization in thalassemia patients: New insight for healthcare. International journal of preventive medicine. 2017;8.

[7] Romphruk AV, Simtong P, Butryojantho C, Pimphumee R, Junta N, Srichai S, Komvilaisak P, Puapairoj C. The prevalence, alloimmunization risk factors, antigenic exposure, and evaluation of antigen-matched red blood cells for thalassemia transfusions: a 10-year experience at a tertiary care hospital. Transfusion. 2019 Jan;59(1):177-84.

[8] El Kababi S, Benajiba M, El Khalfi B, Hachim J, Soukri A. Red blood cell alloimmunizations in beta-thalassemia patients in Casablanca/Morocco: Prevalence and risk factors. Transfusion Clinique et Biologique. 2019 Nov 1;26(4):240-8.

[9] Zheng Y, Maitta RW. Alloimmunisation rates of sickle cell disease patients in the United States differ from those in other geographical regions. Transfusion Medicine. 2016 Jun;26(3):225-30.

[10] Karimi M, Nikrooz P, Kashef S, Jamalian N, Davatolhagh ZR. RBC alloimmunization in blood transfusion-dependent β-thalassemia patients in southern Iran. International journal of laboratory hematology. 2007 Oct;29(5):321-6.

[11] Azarkeivan A, Ansari S, Ahmadi MH, Hajibeigy B, Maghsudlu M, Nasizadeh S, Shaigan M, Toolabi A, Salahmand M. Blood transfusion and alloimmunization in patients with thalassemia: multicenter study. Pediatric hematology and oncology. 2011 Aug 22;28(6):479-85.

[12] Kosaryan M, Mahdavi MR, Roshan P, Hojjati MT. Prevalence of alloimmunisation in patients with beta thalassaemia major. Blood Transfusion. 2012 Jul;10(3):396.

[13] Amin M, Gholamhossein T, Majid N, Marziyeh H, Narges S, Akbar D. Prevalence of alloimmunization against RBC antigens in thalassemia major patients in South East of Iran. J Blood Disorders Transf. 2013;4(147):2.

[14] El-Beshlawy A, Salama AA, El-Masry MR, El Husseiny NM, Abdelhameed AM. A study of red blood cell alloimmunization and autoimmunization among 200 multitransfused Egyptian β thalassemia patients. Scientific Reports. 2020 Dec 3;10(1):1-8.

[15] El Danasoury AS, Eissa DG, Abdo RM, Elalfy MS. Red blood cell alloimmunization in transfusion-dependent Egyptian patients with thalassemia in a limited donor exposure program. Transfusion. 2012 Jan;52(1):43-7.

[16] Ngoma AM, Mutombo PB, Ikeda K, Nollet KE, Natukunda B, Ohto H. Red blood cell alloimmunization in transfused patients in sub-Saharan Africa: A systematic review and meta-analysis. Transfusion and Apheresis Science. 2016 Apr 1;54(2):296-302.

[17] Fateen T, Saqlain N, Mazhar N, Arshad S, Butt S, Malik JZ. Alloimmunization and Autoimmunization in Multi-Transfused Thalassemic Patients: A Single Center Study. Pakistan Journal of Medical & Health Sciences. 2022 Nov 20;16(10):170.

[18] Gehrie EA, Tormey CA. The influence of clinical and biological factors on transfusion-associated non-ABO antigen alloimmunization: responders, hyper-responders, and non-responders. Transfusion Medicine and Hemotherapy. 2014;41(6):420-9.

[19] Kurniawan IR, Prayitno N, Kusumaningrum I, Wiyono S, Meilinasari M. The Role of Intake of Energy, Protein and Parenting with Nutrition Status of Age 12-24 Months in Southern Meruya, West Jakarta. SANITAS: Jurnal Teknologi dan Seni Kesehatan. 2018 Jun 1;9(1):1-5.