RESEARCH ARTICLE
DOI: 10.4274/tjh.galenos.2025.2025.0133

Survey of Red Cell Transfusion Therapy and Immunohematology Service for Patients with Hemoglobinopathies in Turkey

Türkiye'de Hemoglobinopati Hastalarında Eritrosit Transfüzyon Tedavisi ve Immünohematoloji Hizmetleri Araştırması

Gürlek Gökçebay D. et al.: Transfusion Centers Survey for Hemoglobinapathies

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April 11, 2025
July 23, 2025

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Abstract

Objective. Transfusion therapy is critical for many patients with β-thalassemia or sickle cell disease. We aimed to review current practice and document the chronic transfusion therapy for patients with hemoglobinopathies in the transfusion service centers of Turkey.

Materials and Methods. A survey with 16 structured questions was distributed electronically to adult and pediatric hematologists in Turkey. Responses were received from 37 centers across 18 cities, representing 1,449 patients diagnosed with β-thalassemia major, β-thalassemia intermedia, and sickle cell disease.

Results. Although 79% of centers reported performing extended red cell antigen typing prior to the first transfusion, adherence to national transfusion guidelines was inconsistent. Only 16% of centers routinely performed indirect antiglobulin testing before each transfusion, despite guideline recommendations. Antibody identification capabilities varied, with 26% of centers lacking the capability onsite. Elution and adsorption testing were always performed at 13% of centers only, predominantly university hospitals. Nearly half of the centers were always able to provide D,C,E,c,e and Kell compatible red cell units, but one-quarter reported that they were unable to consistently provide compatible units due to limited supply. There was no access to red cell genotyping in the country.

Conclusion. Our survey revealed disparities in transfusion practices and transfusion service laboratory infrastructure across Turkey. There is a need for national policy initiatives to mandate adherence to national and international guidelines, expand immunohematology testing capabilities, and ensure equitable distribution of phenotype-matched red cell units. These data can contribute to a discussion on establishing a centralized immunohematology reference laboratory and enabling red cell genotyping within the country to improve transfusion safety and health equity in hemoglobinopathy care.

Keywords: Thalassemia, sickle cell disease, red cell transfusion, red cell genotyping, immunohematology

ÖZ

Amaç. Transfüzyon tedavisi, β-talasemi veya orak hücre hastalığı olan birçok hasta için kritik öneme sahiptir. Bu çalışmada, Türkiye'deki transfüzyon merkezlerinde hemoglobinopatili hastalara yönelik kronik transfüzyon tedavisinin güncel uygulamalarını ortaya koymayı amaçladık.

Gereç ve Yöntem.. Türkiye'deki yetişkin ve pediatrik hematologlara 16 sorudan oluşan yapılandırılmış bir anket elektronik olarak gönderildi. Yanıtlar, 18 ildeki 37 merkezden, β-talasemi major, β-talasemi intermedia ve orak hücre hastalığı tanısı almış 1449 hastayı kapsayacak şekilde alındı.

Sonuçlar. Merkezlerin %79'u ilk transfüzyondan önce genişletilmiş eritrosit antijen tiplendirmesi yaptığını bildirmiş olsa da, ulusal transfüzyon kılavuzlarına uyum tutarsızdı. Kılavuz önerilerine rağmen, merkezlerin sadece %16'sı her transfüzyondan önce rutin olarak indirekt antiglobulin testi yaptığını bildirdi. Antikor tanımlama testi olanakları çeşitlilik göstermekte olup, merkezlerin %26'sında bu olanak bulunmamaktaydı. Elüsyon ve adsorpsiyon testleri, çoğunluğu üniversite hastaneleri olmak üzere merkezlerin yalnızca %13'ünde her zaman yapılabilmekteydi. Merkezlerin yaklaşık yarısı hemoglobinopati hastalarına her zaman D,C,E,c,e ve Kell uyumlu eritrosit konsantreleri

sağlayabiliyordu, ancak dörtte biri yetersiz tedarik nedeniyle devamlı olarak uyumlu eritrosit sağlayamadıklarını bildirdi. Ülkede eritrosit genotipleme yapılamamaktaydı.
Sonuç. Araştırmamız Türkiye genelinde transfüzyon uygulamaları ve kan bankası laboratuvar altyapısı açısından farklılıklar olduğunu ortaya koymuştur. Standardize transfüzyon protokollerine uyulmasını zorunlu kılmak, immünohematoloji test olanaklarını genişletmek ve fenotipik uyumlu eritrosit konsantrelerinin her bölgeye dağıtımını sağlamak için ulusal politika geliştirilmesine ihtiyaç vardır. Hemoglobinopati tedavisinde transfüzyon güvenliğini ve sağlıkta eşitliği iyileştirmek için merkezi bir immünohematoloji referans laboratuvarının kurulmasına ve ülkemizde eritrosit genotiplemesinin etkinleştirilmesine öncelik verilmelidir.
Anahtar kelimeler. Talasemi, orak hücre hastalığı, eritrosit transfüzyonu, eritrosit genotipleme, immunohematoloji

Introduction

Hemoglobinopathies are a group of inherited blood disorders characterized by abnormalities in the hemoglobin molecule that can result in an impaired ability to transport oxygen leading to hemolysis.[1] The absence or diminished synthesis of β-globin in β-thalassemia major or intermedia results in a shortened lifespan of red cells; these patients should receive regular red cell transfusions for normal growth and development. The clinical features of sickle cell disease (SCD) reflect the tendency of erythrocytes to adopt a sickle shape in deoxygenated blood, resulting in reduced red cell survival and a tendency to block small blood vessels. Therefore, red cell transfusion is a critical therapeutic intervention for avoiding certain complications of SCD.[2]

Turkey has made progress in the safe provision and use of blood and blood products under the Blood and Blood Products Law (2007), followed by the Implementing Regulation on Blood and Blood Products (2008), the Guide on Blood and Blood Products (2009), National Guides on Preparation, Use and Quality Assurance of Blood Components (2016), Standards for Blood Service Units (2016), the Quality Management System for Blood Service Units (2016), and Hemovigilance (2020). Turkey is an active member of the Council of Europe, and the national guidelines are in compliance with the European Union legislation on blood and blood products. The Turkish Red Crescent has the main responsibility with 13 temporary regional blood centers related to blood supply throughout the country to collect and process voluntary blood donations. Adult or pediatric hematology clinics are established in 75 of the 81 provinces of Turkey.[3] Hematologists and transfusion medicine specialists are actively involved in optimizing transfusion care through the use of uniform blood bank practices across the country.

According to the International Thalassemia Federation (TIF), the Turkish Thalassemia Diagnosis and Follow-up guideline, and the American Society of Hematology (ASH) guideline for SCD, patients should have extended red cell antigen typing, at least including ABO, D,C,c,E,e and Kell before starting transfusion therapy.[4,5,6] All patients with transfusion dependent β-thalassemia major and intermedia should be transfused with ABO, D,C,E,c,e and Kell compatible, leukocyte-reduced red cells in a volume of 10 - 15 mL/kg every 3 - 4 weeks.[4,5] Antibody screening should also be performed before each transfusion, as alloimmunization rates have been reported to range from 2.9% to 37% in various populations.[7]

We aimed to survey the current practice and document the chronic transfusion therapy for patients with hemoglobinopathies in the transfusion service centers of Turkey.

Materials and Methods

Participants. Survey participants were recruited by the members of the Turkish Society of Hematology. Pediatric hematologists who are members of the Turkish Society of Pediatric Hematology also participated in the survey. Invitation e-mails were repeatedly sent to approximately 600 specialists of adult or pediatric hematology between January 15 and February 15, 2025. Respondents from 37 centers – of a total of 75 centers – voluntarily participated in the survey – representing 5 of 7 geographical regions in Turkey – and replied to subsequent correspondence (Table 1). Respondents consented to voluntary participation and became authors as the Turkish Hemoglobinopathy Survey Investigators. The demographics of the non-respondents remained unknown. Hence, no ethics approval for human subjects research was required.

All e-mails provided a link to a website for an electronic version of the survey (Table S1).

Questionnaire. Prospective participants received a questionnaire (Table S1). We requested information for: 1) number of patients with β-thalassemia major, intermedia, and SCD receiving regular red cell transfusions or exchange transfusions at each institution; 2) required pre-transfusion serologic testing of the patients with hemoglobinopathy, such as C,E,c,e and Kell; 3) frequency of direct antiglobulin test (DAT) and indirect antiglobulin test (IAT) and interpretation of the results; 4) routine use of antibody identification, elution and adsorption tests and interpretation of such results; and 5) information on the rate of supply of C,E,c,e and Kell compatible red cell units for patients with hemoglobinopathies.

Results and Discussion

A total of 20 adult hematology specialists (54%) and 17 pediatric hematology specialists (46%) from 37 centers in 18 cities in Turkey responded to the survey (Table 1). The 3 most populated cities in Turkey, Istanbul, Ankara, and Izmir, accounted for 38% of the responding centers. Among participating centers, 17 were university hospitals (46%), 17 public or city hospitals (46%), and 3 private hospitals (8%); 12 centers were located in the Marmara region (32%), 10 centers in the Central Anatolia region (27%), 8 in the Mediterranean region (22%), 6 in the Aegean region (16%), and 1 in the Southeastern Anatolia region (3%) of Turkey. When contacting the specialists in the Black Sea region, they responded verbally that they didn't have any patients with hemoglobinopathy and regular transfusion (not shown). No data were received from the Eastern Anatolia region. Our statement is supported by a previous study indicating that the Black Sea region had no recorded cases of thalassemia, while the Eastern Anatolia region had the lowest number of documented patients with thalassemia.[8] Hence, a possible impact of missing data from Eastern Anatolia and Black Sea regions was limited. The overall response rate for our 16 questions was 97%. We collated data for 1449 patients, including 1226 with β-thalassemia major (85%), 130 with β-thalassemia intermedia (9%), and 93 with SCD (6%) from 37 centers (Table 1). Ankara (Bilkent City Hospital), Izmir (Ege University), and Antalya (Akdeniz University) pediatric hematology outpatient clinics reported 440 patients with β-thalassemia major (34%), while most adult β-thalassemia major patients (18%) were reported from Istanbul (Istanbul University) and Hatay (Iskenderun Public Hospital) hematology clinics. Similarly, β-thalassemia intermedia patients were mostly from Istanbul, Izmir, Antalya, and Konya. However, more than half of the patients with SCD (52%) were followed at Antalya, Hatay, Mugla, and Istanbul adult hematology outpatient clinics. Previous epidemiologic studies from Turkey reported that the Mediterranean region was most prevalent for SCD and coastal areas for β-thalassemia,[9,10] which we corroborated in our survey.

Red cell phenotyping. Phenotyping for C,E,c,e and Kell was always performed in most of the centers (79%) before the first transfusion (Table 2). When transfused patients with hemoglobinopathy were referred from another center, 27 centers (71%) always performed the C,E,c,e and Kell typing, too. Although the 2 existing thalassemia guidelines for Turkey recommend extended red cell antigen typing, including ABO, D,C,c,E,e and Kell, before starting transfusion therapy, 2 adult hematology centers (5%) reported performing extended phenotyping neither for patients diagnosed at their center nor for those referred from other centers. This finding suggested gaps in the adherence to established guidelines. A previous study from the United States revealed inconsistencies in transfusion practices between thalassemia or sickle cell comprehensive care centers and other healthcare institutions. Notably, only 20% of non-thalassemia treatment centers and 71% of non-sickle cell treatment centers were reported to follow established guidelines by providing Rh- and Kell-matched red blood cell units prophylactically.[11] The hemoglobinopathy survey in England also revealed suboptimal compliance with transfusion guidelines, with only 71% of the patients being phenotyped for Rh and Kell antigens.[12] These data highlight potential areas for improvement of transfusion practices, particularly to ensure compatibility and prevent alloimmunization among hemoglobinopathy patients.

The transfusion policy for patients referred from another center, who were tested for D,C,c,E,e and Kell and had a mixed-field reaction, was to transfuse cross-match compatible red cell units in 12 centers (32%) and red cell units negative for mixed-field antigens in 10 centers (27%), to review old subgroup results from the referring center in 4 centers (11%), to consult an experienced center in 3 centers (8%), and to perform DAT, IAT, and antibody identification tests in 2 centers (5%). Another 6 centers (16%) reported having encountered no mixed-field reaction.

DAT and IAT testing. The frequency of performing DAT and IAT testing varied widely among centers (Table 3). Before the first transfusion, less than one-third of the centers performed either test. For ongoing transfusion therapy, 62% of the centers reported performing DAT at least once a year. Although the TIF guideline and the Appropriate Clinical Use of Blood Guide recommend IAT testing before every transfusion,[4,13] only 6 university hospitals (16%) performed an IAT before every transfusion. While many specialized centers were cautious about ensuring compatibility through DAT and IAT testing (not shown), all centers should follow consistent protocols impacting patient safety, such as preventing alloimmunization and hemolytic transfusion reactions.[14]

Transfusion and typing strategies for DAT-positive patients also varied highly (Table 4). Only 6 centers (16%) reported giving cross-matched and C, E, c, e and Kell compatible red cell units, investigating the cause of DAT positivity, and performing elution. An additional 9 centers followed a similar strategy without elution (24%). This suggests that elution, a technique used to detect red cell-bound antibodies, was not widely utilized across the country. Another 6 centers relied solely on cross-match-compatible red cell units without additional antigen matching (16%), while 4 centers provided red cell units matched only for C, E, c, e and Kell (11%).

Elution and antibody identification testing. Almost two-thirds of centers (63%) reported being unable to perform elution and adsorption tests (Table 1). Conversely, only 5 centers (13%) consistently performed these tests, with the majority being university hospitals and one being a training and research hospital. Currently, these specialized tests

seem largely dependent on institutional resources and expertise. A national resource and an immunohematology reference laboratory could serve for these non-urgent tests.

Regarding antibody identification, 18 centers always performed this test (47%), whereas 10, mostly city/ or public, hospitals lacked this capability onsite (26%) and sent their samples to university hospitals (n = 8) or laboratory companies (n = 2). These findings highlight disparities in laboratory capabilities, which can delay transfusion decisions and patient management. Furthermore, the ability to provide antigen-negative red cell units compatible with antibody identification results was limited, with only 5 centers always (13%), 14 usually (38%), and 13 sometimes (35%) able to supply antigen-negative red cell units based on antibody identification results. As a result, they were able to provide antigen-matched red cells to 42% of their hemoglobinopathy patients based on antibody identification results. However, 5 centers could not provide antigen-matched red cell units based on antibody identification results (13%).

Supply of compatible red cell units. Many centers (n = 17) could always provide C, E, c, e and Kell compatible red cell units for thalassemia patients (n = 16) and for alloantibody positive patients (n = 1). However, 9 centers reported that they were not able to consistently provide compatible red blood cells to patients with hemoglobinopathies due to a shortage of supply, 13 centers usually provided C, E, c, e and Kell compatible red cell units for thalassemia (n = 2) and SCD patients (n = 2), and 6 centers sometimes provide for alloantibody (n = 4) or DAT positive patients (n = 1). Only 1 center responded not providing compatible red cell units at all, with transfusions limited to DAT-positive patients. These data highlight disparities in transfusion practices and emphasize the need for policy interventions aimed at improving the availability and equitable distribution of phenotype-matched red blood cell units across transfusion service centers.

Red cell genotyping. Only 1 center reported sending samples to another country in Europe for red cell genotyping in some cases of complicated alloantibodies in thalassemia patients. No center provided red cell genotyping practice for their patients onsite or had access to red cell genotyping within Turkey.

Conclusion. This nationwide survey provided a comprehensive overview of current transfusion practices for patients with hemoglobinopathy across 37 centers in Turkey. Our survey nearly equally represented adult and pediatric hematology specialists. Despite national and international guidelines recommending extended red cell antigen phenotyping and antibody screening,[4,5] our findings revealed significant variability in the implementation of this recommendation. While the majority of centers performed initial phenotyping and strive to provide C, E, c, e and Kell compatible red cell units, key practices — such as routine IAT testing before each transfusion, the use of elution techniques, and access to antibody identification — are inconsistently applied and often limited by institutional resources. In addition, blood group identification can be complicated by the lack of antigen typing before the first transfusion, because of mixed field reactions after recent transfusion.

One-fourth of the centers explicitly cited supply limitations as the primary reason for not consistently providing antigen-matched red cell units. This constraint represented a significant systemic barrier to optimal transfusion care and increased the likelihood of alloimmunization and hemolytic transfusion reactions. This inequity of access to patient care was particularly concerning regions with limited immunohematology infrastructure, suggesting the urgent need for a centralized coordination and supply chain improvement. The documented data may be used to evaluate the feasibility, cost-effectiveness, and impact on the healthcare system of proposed changes, such as a centralized immunohematology reference laboratory and red cell genotyping, in Turkey. Developing a centralized policy that mandates red cell antigen typing, alloantibody screening, and red cell genotyping — especially in cases with alloantibodies or complex serology — integrated with the Turkish Red Crescent and regional blood banks, may help address these gaps.

Acknowledgement. We thank the members of the Turkish Society of Hematology, Scientific Subcommittee of Transfusion Medicine-Blood Banking and Hemapheresis, and the Turkish Society of Pediatric Hematology, Scientific Subcommittee of Apheresis/Transfusion, for their active participation.

Conflict of interest disclosure. The authors declared having no competing financial interest.

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Authorship contribution. DGG, NA and WAF designed the study approach and developed the rationales. The Turkish Hemoglobinopathy Survey Investigators provided all data collected in this survey. DGG gathered all

information of the survey responses. DGG analyzed the data with WAF. DGG and WAF discussed the data and wrote the final manuscript.

Funding. This work was supported by the Intramural Research Program (ZIC CL002128) of the NIH Clinical Center at the National Institutes of Health and TUBITAK 2219 Postdoctoral Research Project (1059B192301778).

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monospecific autoanti-JK(b) in intermediate β-thalassemia patient in Tabriz. Asian J Transfus Sci. 2013;7(2):149-150

Table 1. Geographic regions in Turkey and patients reported by survey respondents

	Patients					
	β-thalassemia				Sickle cell disease	
Regions*	Major (n)	Intermedia (n)	Total	%	n	%
Marmara	261	29	290	21%	22	24
Central Anatolia	270	24	294	22%	11	12
Mediterranean	320	52	372	27%	38	41
Aegean	280	15	295	22%	20	21
Southeast Anatolia	95	10	105	8%	2	2
Black Sea	nr	nr	nr	nr	nr	nr
East Anatolia	nr	nr	nr	nr	nr	nr
Total	1226	130	1356	100%	93	100%

* Geographic regions tabulated by population size
nr - no responses received

Table 2. Routine serologic testing for patients with hemoglobinopathies in Turkey

	Transfusion Service Centers							
	CEce and Kell antigens							
	Diagnosed at the center		Referred from another center		Antibody identification		Adsorption and elution	
Responses	n	%	n	%	n	%	n	%
Always	29	79%	26	71%	18	47%	5	13%
Usually	5	13%	9	24%	5	16%	3	8%
Sometimes	1	3%	0	2%	4	11%	6	16%
Never	2	5%	2	5%	10	26%	23	63%
Total	37	100%	37	100%	37	100%	37	100%

Table 3. Frequency of performing direct antiglobulin (DAT) and indirect antiglobulin test (IAT) in patients with hemoglobinopathies

	Transfusion Service Centers			
	DAT		IAT	
Frequency	n	%	n	%
Before first transfusion only	11	30%	10	27%
Before every transfusion	3	8%	6	16%
Once per year	7	19%	9	24%
2 times a year	7	19%	9	24%
4 times a year	9	24%	3	8%
Total	37	100%	37	100%

Table 4. Transfusion strategies direct antiglobulin testing

	Transfusion Service Centers (n)* and answers†									
Questions	6	9	4	2	2	1	1	6	4	2
I give cross-match compatible red cell units	x	x		x	x			x		
I give C,E,c,e, and Kell compatible red cell units	x	x	x		x	x			x	
I investigate the reason for DAT positivity	x	x	x	x			x			x
Elution should be done	x					x	x			

* For a total of 37 centers

† 10 different response patterns are shown along with the number of centers (n=1 to n=9) responding in 1 of the 10 possible response patterns.