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Blood transfusion compliance in children with transfusion-dependent Thalassemia

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Abstract: Children with transfusion-dependent thalassemia (TDTs) need regular blood transfusions and maintain a 9-10 g/dl hemoglobin level. Unfortunately, blood transfusion implied iron overload, characterized by increased serum ferritin levels and iron accumulation in the tissues and blood as serum ferritin. This study evaluated the differences in serum ferritin levels in children with TDTs who were compliant and non-compliant with transfusion based on transfusion compliance. The cross-sectional study evaluated children with TDTs (5-18 years). The child would come for routine blood transfusions every 2-6 weeks. Low blood compliance was defined as children with a hemoglobin level below 7.0 g/dL at least three times during the last ten visits. We evaluate ferritin levels every three months. We use the Chi-Square test with $p<0.05$ for the two-tail test. About 67 TDTs children met the criteria; 55.2% were male, and 56.2% were adolescents. The mean hemoglobin level was 7.9 (SD 0.47) g/dL. About 27 (30.3%) children had non-compliance, and 62(69.7%) were good compliance. About 51.9% of children come every two weeks for blood transfusions in the non-compliance group, and 64.5% come every four weeks in the good compliance group with $p=0.038$. The mean ferritin level in the non-compliance group was higher than good compliance: 2656.0 (1241.58) ng/mL compared to 2123.7 (SD 1231.61) ng/mL with $p=0.027$. Most children in non-compliance (51.9%) had serum ferritin levels above 2500 mg/dL, and 52.8% in good compliance had ferritin 1000-2500 ng/mL with $p=0.024$. Feritin level in children with TDT with non-blood transfusion compliance was higher than reasonable.

Keywords: *Blood transfusion, Child, Compliance, Ferritin, Thalassemia.*

1. Introduction

Thalassemia is a hereditary genetic disease spreading worldwide, especially in the Mediterranean, Middle East, India, Pakistan, and Southeast Asia [1, 2]. The disrupted hemoglobin polypeptide chain type will determine the type of thalassemia [3]. Thalassemia syndrome consists of α-thalassemia, β-thalassemia, and hemoglobin-E diseases, with prevalence ranging from 2.5% to 15% in Southeast Asia [2]. The prevalence of thalassemia-carrying genes in Indonesia varied from 1-33% [4]. East Java also has a heterogeneous genetic variation of thalassemia [5, 6]. The frequency of the thalassemia trait gene is 3-10%. The number of thalassemia cases recorded at the Division of Hematology-Oncology, Dr. Soetomo General Academic Hospital, Surabaya, has been increasing yearly. The number of children with thalassemia between 2009-2013 recorded 267 patients. Most cases were β thalassemia, β-thalassemia/HbE diseases, and a small proportion of α-thalassemia [7].

The clinical classifications of thalassemia were transfusion-dependent thalassemia (TDTs) and non-transfusion-dependent thalassemia (NTDT). Clinical manifestations of TDTs can appear at 6-24 months, characterized by paleness, hepatosplenomegaly, and failure to thrive [4, 8]. Children with TDTs usually require blood transfusions at least once every 2-6 weeks to maintain Hb levels above 9.0-10.5 g/dL. Regular PRC transfusions will reduce ineffective complications of anemia and erythropoiesis,

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help growth and development, and extend life expectancy [8, 9]. The most common complications are endocrinopathy, cardiac iron overload, and liver iron overload [10-13].

Regular blood transfusions and iron chelation are currently the spearheads in managing thalassemia. Regular transfusion will reduce the risk of complications related to severe anemia and survival. Blood transfusion aims to correct anemia, suppress erythropoiesis, and inhibit gastrointestinal iron absorption[8]. Repeated transfusions may cause iron overload (hemosiderosis) in several organs [9, 14]. Inadequate blood transfusions can cause extramedullary hematopoiesis, growth retardation, bone abnormalities, skeletal osteoporosis, and fractures [9, 14]. Iron chelation therapy begins with a transfusion of 10-20 units of blood and a serum ferritin level of 1,000ug [15, 16]. This study evaluates the blood transfusion compliance and serum ferritin levels in children with transfusion-dependent thalassemia.

2. Material and Methods

This cross-sectional study evaluated children with TDTs aged 5 to 18 at the Pediatric Hematology-Oncology outpatient clinic, Department of Child Health, Dr. Soetomo General Academic Hospital, Surabaya, East Java, Indonesia, from August to October 2022. This research has received ethical approval from the Dr. Soetomo General Academic Hospital Surabaya—Health Research Ethics Committee (KEPK) with a letter of exception 0462/KEPK/VIII/2022.

The diagnosis of thalassemia is established based on clinical manifestations, hematological examination (complete blood count, red cell index, peripheral blood smear, serum iron, and ferritin levels), and hemoglobin analysis. The TDTs generally occur in children under two years old with severe microcytic anemia, jaundice, and hepatosplenomegaly. Hemoglobin (Hb) levels under 7 g/dL, mean corpuscular volume (MCV) 50-70 fL, and positive results for high-performance liquid chromatography (HPLC) techniques from peripheral blood samples confirm the diagnosis. The TDTs will get blood transfusions every 2-6 weeks to maintain hemoglobin levels above 9-10.5 g/dL. The categories of thalassemia in this group are β-thalassemia major, severe HbE/β-thalassemia, and transfusion-dependent HbH disease.) Children with TDTs usually start blood transfusions before the age of 2 years. The diagnosis of thalassemia is determined by a Consultant Hematology Oncologist.

The sample size calculation was based on the proportion data test formula. The magnitude of $Z1-1/2\alpha$ is 1.96 for the two-tailed test, and the power of the test is set at 80%, so Z1-ß is 0.842. Based on the formula, the study required at least 78 children. We excluded children receiving regular blood transfusions outside our institution. Other exclusion criteria included congenital heart defects, cancer history, Down syndrome, autoimmune diseases, and other congenital anomalies. We also excluded children with a history of autoimmune hemolytic anemia, autoantibodies, alloantibodies, and splenectomies.

Routine checks at each visit included a complete blood count evaluation using the Sysmex® XP-100 Hematology Analyzer. If the hemoglobin level was less than 9.0 g/dL, the child received a blood transfusion of 10-15 mL per kg body weight, aiming for a post-transfusion hemoglobin target of 11-12 g/dL using leukoreduced PRC. Children with hemoglobin above 7.0 g/dL were given transfusions at a one-day care clinic. The blood bank institution provided the blood supply, ensuring an adequate and safe supply for all patients requiring transfusions. Children with hemoglobin levels less than 7.0 g/dL or hemoglobin above 7.0 g/dL with complications were given transfusions in the inpatient room. These complications included a history of severe transfusion reactions and seizures.

The average hemoglobin level was calculated from the last ten visits. The number of visits with hemoglobin levels below 7.0 g/dL reflected transfusion regularity. Children were considered non-compliant with transfusions if they had at least two instances of pre-transfusion hemoglobin below 7.0 g/dL in the last ten visits.

Serum ferritin levels were measured using the Enzyme-Linked Fluorescent Assay (ELFA) technique with the Vidas tool at least once every three months. Ferritin levels were categorized as low (ferritin

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<1000 µg/L), high (ferritin 1000-2500 µg/L), and very high (ferritin >2500 µg/L), with the average of the last three tests used for analysis.

Factors influencing transfusion regularity included age, sex, frequency of transfusions, and type of iron chelation. Children were grouped as childhood (under ten years) and adolescence (over ten years). Residence was categorized as urban or rural, and the distance between the home and the hospital was classified as less than 10 km or more than 10 km. Transfusion frequency reflected the distance between visits to the hospital, i.e., the number of weeks it took to get the subsequent blood transfusion. Psychosocial aspects of children and families were not evaluated. We used the Statistical Package for the Social Sciences (SPSS) 18 for Windows. The mean difference in serum ferritin levels between compliant and non-compliant groups was analyzed using the independent sample t-test if the data were normally distributed (verified with the Kolmogorov-Smirnov test) and the Mann-Whitney U test if the data were not normally distributed. The level of significance was set at $p<0.05$ for a two-tailed test.

3. Results

Our institution had 267 registered children with thalassemia. We distributed 110 questionnaires and received 93 responses. Four children had incomplete questionnaires. We excluded 19 children due to the following reasons: under 5 years old (9), hemoglobin data available for less than 10 visits (3), and ferritin levels measured only 1 or 2 times (10). The remaining 67 children with transfusion-dependent thalassemia (TDT) were included in the study. The characteristics of the research subjects are shown in Table 1.

Table 1.
Characteristics of research subjects in children with TDTs.

Variable	N	%
Sex		
Boys	37	55.2
Girls	30	44.8
Age category		
<10 years	23	34.3
≥10 years	44	65.7
Ethnic group		
Javanese	62	92.5
Madurese	5	7.5
Residence		
Surabaya	21	31.3
Outside Surabaya (Out of town)	46	68.7
Time to the hospital		
<1 hour	44	65.7
≥1 hour	23	34.3
Distance from hospital		
<10 km	50	74.6
≥10 km	17	25.4
Transportation		
Private vehicle	51	76,1
Public/rental transportation	16	23.9
Family income		
Under minimum wage	30	44.8
Above minimum wage	37	55.2

Most children were male (55.2%) and over 10 years old (65.7%). Javanese were the majority of the study subjects (92.5%), and 68.7% lived outside Surabaya. Most children lived in houses less than 10 km away from the hospital (74.6%), with a travel time of less than 1 hour (65.7%), primarily using private vehicles (76.1%). Regarding family income, 44.8% of children came from families with incomes below the regional minimum wage.

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The average hemoglobin level over the last 10 visits was 7.9 (SD 0.40) g/dL. Most children had hemoglobin levels between 7 g/dL and 9 g/dL, with the lowest level recorded at the fourth visit (76.1%) and the highest at the first visit (86.5%). The average hemoglobin level over the last 10 visits was 95.5% in the 7-9 g/dL range. The number of children with hemoglobin levels above 11 g/dL occurred in only one child, during the third visit. Data on children's hemoglobin levels can be seen in Table 2.

Table 2.
Hemoglobin levels based on visits time.

Measurement	Hemoglobin level (g/dL)		Hemoglobin groups g/dL			
	Mean (SD)	Median (Min.-Max.)	<7 N(%)	7-<9 N(%)	9-<11 N(%)	≥11 N(%)
Measurement-1	8.0 (0.72)	8.0 (6.9-10.7)	5 (7.5)	58 (86.5)	4 (6.0)	0
Measurement -2	7.9 (0.72)	8.0 (5.7-9.3)	7 (10.4)	54 (80.6)	6 (9.0)	0
Measurement -3	7.9 (0.79)	8.1 (6.4–11.2)	10 (14.9)	52 (77.6)	4 (6.0)	1 (1.5)
Measurement -4	8.0 (0.93)	8.0 (4.9-10.6)	8 (11.9)	51 (76.1)	8 (11.9)	0
Measurement -5	7.8 (0.79)	7.9 (5.4-9.6)	8 (11.9)	54 (80.6)	5 (7.5)	0
Measurement -6	7.9 (0.75)	8.0 (5.8-9.9)	8 (11.9)	54 (80.6)	5 (7.5)	0
Measurement -7	7.9 (0.98)	7.9 (5.7-10.5)	10 (14.9)	49 (73.1)	8 (11.9)	0
Measurement -8	7.9 (0.72)	8.0 (6.0-9.7)	6 (9.0)	55 (82.1)	6 (9.0)	0
Measurement -9	7.8 (0.75)	7.8 (5.8-9.7)	11 (16.4)	53 (79.1)	3 (4.5)	0
Measurement-10	7.9 (0.81)	7.9 (5.7-10.7)	6 (9.0)	57 (85.1)	4 (6.0)	0
Mean	7.9 (0.40)	7.9 (6.7-9.1)	2 (3.0)	64 (95.5)	1 (1.5)	0

Note: Min-Max = Minimum-Maximum.

As many as 32 out of 67 children, or 47.8%, never presented with hemoglobin (Hb) levels less than 7 g/dL. About 33.9% of children, at least once, had Hb <7 g/dL, and 11.9% had Hb levels <7 g/dL on two occasions. One interesting finding was that one child had Hb levels consistently below 7 g/dL in 9 out of 10 visits. Data on visits with Hb levels less than 7 g/dL can be found in Table 3.

Table 3.
Number of visits with Hb<7 g/dL.

Number of visits	N	%
0	32	47.8
1	16	23.9
2	8	11.9
3	5	7.5
4	3	4.5
5	1	1.5
6	1	1.5
7	0	0
8	0	0
9	1	1.5
10	0	0

Good compliance with transfusion occurred in 48 out of 67 children (71.6%). Meanwhile, 28.4% of children were classified as non-compliant, as they presented with hemoglobin (Hb) levels below 7 g/dL on at least two occasions during their last ten visits. Data on the role of demographic factors in transfusion compliance among children with transfusion-dependent thalassemia are shown in Table 4 below.

There was no significant difference in compliance levels between boys and girls (p=0.172) or between children aged below and above 10 years (p=0.399). Similarly, compliance levels did not differ significantly between Javanese and other ethnic groups, nor between children living in Surabaya and those residing outside the city. Travel time and distance from home to the hospital also showed no significant differences between compliant and non-compliant children (p=0.785 and p=0.760,

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respectively). Furthermore, the type of transportation used to reach the hospital and parental income levels were not associated with differences in transfusion compliance.

Table 4.
Baseline characteristics of study subjects based on transfusion compliance in children with TDTs.

Variable	Transfusion compliance rate		Total (n=67)	p
	Compliant (n=48)	Non-compliant (n=19)		
Sex				
Boys	24 (50.0)	13 (68.4)	37 (55.2)	0.172[a]
Girls	24 (50.0)	6 (31.6)	30 (44.8)	
Age category				
<10 years	15 (31.3)	8 (42.1)	23 (34.3)	0.399[a]
≥10 years	33 (68.7)	11 (57.9)	44 (65.7)	
Ethnic group				
Javanese	44 (91.7)	18 (94.7)	62 (92.5)	1.000[b]
Madurese	4 (8.3)	1 (5.3)	5 (7.5)	
Residence				
Surabaya	17 (35.4)	4 (21.1)	21 (31.3)	0.253[a]
Outside Surabaya (out of town)	31 (64.6)	15 (78.9)	46 (68.7)	
Time to the hospital				
<1 hour	32 (66.7)	12 (63.2)	44 (65.7)	0.785[a]
≥1 hour	16 (33.3)	7 (36.8)	23 (34.3)	
Distance from hospital				
<10 km	35 (72.9)	15 (78.9)	50 (74.6)	0.760[b]
≥10 km	13 (27.1)	4 (21.1)	17 (25.4)	
Transportation				
Private vehicle	37 (77.1)	14 (73.7)	51 (76.1)	0.760[b]
Public/rental transportation	5 (26.3)	11 (22.9)	16 (23.9)	
Family income				
Under minimum wage	21 (43.8)	9 (47.4)	30(44.8)	0.788[a]
Above minimum wage	27 (56.3)	10 (52.6)	37 (55.2)	

Note: [a]chi-square tests and [b]Fisher exact test,

The mean serum ferritin levels across three measurements are presented in Table 5 below. The mean ferritin levels ranged from 2,164 ng/mL to 2,447.3 ng/mL. The lowest ferritin level recorded was 400.0 ng/mL in the third examination, while the highest was 10,906.7 ng/mL in the second examination. The overall mean ferritin level from the three measurements was 2,340.3 ng/mL, with a standard deviation of 1,138.91 ng/mL.

Among the children studied, 50.7% had moderate ferritin levels (between 1,000 ng/mL and 2,500 ng/mL). Meanwhile, 10.4% of children had low ferritin levels, and 38.8% had high ferritin levels.

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Table 5.
Serum ferritin levels in children with TDTs.

Examination	Serum Ferritin (ng/mL)		Serum ferritin categorise ng/mL n (%)		
	Mean (SD)	Median (Min.-Max.)	<1,000	1,000-2,500	>2,500
1st Visit	2,164.7 (1,373.13)	1,856.7 (217.7-8,400.0)	11 (14.4)	39 (58.2)	17 (25.4)
2nd Visit	2,408.8 (1,655.17)	2,261.6 (499.4-10,906.7)	13 (19.4)	29 (43.3)	25 (37.3)
3rd Visit	2,447.3 (1,556.24)	2,154.0 (400.0-8,961.0)	8 (11.9)	34 (50.7)	25 (37.5)
Mean	2,340.3 (1,138.91)	2,151.0 (587.6-5,981.5)	7 (10.4)	34 (50.7)	26 (38.8)

Note: Min-Max: Minimum-Maximum.

The average ferritin level in children compliant with transfusion was lower than in non-compliant children, at 2,165.4 ng/mL compared to 2,781.9 ng/mL, with a statistically significant difference (p=0.045). In children who were compliant with transfusion, most had ferritin levels between 1,000 ng/mL and less than 2,500 ng/mL.

In contrast, the ferritin levels in non-compliant children showed an inverse pattern compared to the compliant group, with 57.9% having ferritin levels above 2,500 ng/mL. Additionally, the proportion of children with low ferritin levels (below 1,000 ng/mL) was higher in the compliant group compared to the non-compliant group, at 12.5% versus 5.3%, with a significant difference (p=0.046).
Detailed data on ferritin levels based on transfusion compliance is presented in Table 6 below.

Table 6.
Ferritin levels in children with TDTs based on transfusion compliance level.

Serum ferritin level	Blood transfusion compliant		Total (n=67)	p
	Compliant (n=48)	Non-compliant (n=19)		
Serum ferritin[a]				
Mean (SD)	2,165.4 (1,099.75)	2,781.9 (1,144.83)	2,340.3 (1,138.91)	0.045[b]
Median (min-maks)	1,982.0 (710.0-5,981.4)	2,844.1 (587,5-5,609.6)	2,151.0 (587.6-5,981.5)	
Ferritin categorizes				
<1000 ng/mL	6 (12.5)	1 (5.3)	7 (10.4)	0.046[c]
1000 to <2500 ng/mL	27 (56.3)	7 (36.8)	34 (50.7)	
>2500 ng/mL	15 (31.3)	11 (57.9)	26 (38.8)	

Note: [a] Two-Sample Kolmogorov-Smirnov Test, [b] Independent sample t-test, [c] Mann-Whitney U test Test

Most children (64 out of 67, or 95.5%) used iron chelation therapy, with deferiprone being the most commonly used chelator (41 out of 64, or 64.1%), followed by deferasirox (23 out of 64, or 35.9%). Transfusion compliance differed significantly based on the use of iron chelation.

Children compliant with transfusion who used iron chelation had lower median ferritin levels compared to non-compliant children who also used iron chelation, with values of 2,032.5 ng/mL versus 2,844.1 ng/mL, though the difference was not statistically significant (p=0.083).

Among children using deferasirox, there was no significant difference in median ferritin levels between compliant and non-compliant groups (p=0.325). Similarly, no significant difference in median ferritin levels was observed between compliant and non-compliant groups using deferiprone (p=0.183). Complete data can be found in Table 7.

Table 7.
Median serum ferritin levels in children with TDTs.

Iron chelation	N	Serum ferritin level Median (Min.-Max.) mcg/L		Total Median (Min.-Max.) ng/mL	ρ
		Compliant	Non-compliant		
Iron chelation [a]					
N		19	45		
Yes	64	2,032.5 (710.0-5,981.5)	2,844.1 (587.6-5,906.7)	2,201.2 (587.6-5,981.5	0.083[c,d]
None	3	898.0 (763.3-921.0)	None	898.0 (763.3-921.0	NA
				p=0.001[a,b]	
Iron chelation					
n		8	15		
Deferasirox	23	1,937.0 (959.3-5,981.5)	2,722.0 (1,579,7 (1,579.7-5,609.7)	2,151.0 (959.3-5,981.4)	0.325[g,h]
n		11	30		
Deferiprone	41	2,116.5 (710.0-4,336.5	2,844.1 (587.5-4,372.3)	2,235.9 (587.5-4,372.3)	0.183[i,j]
				Nilai p=0,613[e,f]	

Note: [a] *Two-Sample Kolmogorov-Smirnov Test* (abnormal distribution, serum ferritin level between iron chelation yes or none), [b] *Mann-Whitney U test Test* (serum ferritin level between iron chelation yes or none), [c] *Two-Sample Kolmogorov-Smirnov Test* (normal distribution, serum ferritin level between compliant and non-compliant in iron chelation group), [d] *Independent sample t-test* (serum ferritin level between compliant and non-compliant in iron chelation group), [e] *Two-Sample Kolmogorov-Smirnov Test* (abnormal distribution, serum ferritin level between deferasirox and deferiprone), [f] *Mann-Whitney U test Test* (serum ferritin level between deferasirox and deferiprone), [g] *Two-Sample Kolmogorov-Smirnov Test* (abnormal distribution, serum ferritin level between compliant and non-compliant in deferasirox group), [h] *Mann-Whitney U test Test* (abnormal distribution, serum ferritin level between compliant and non-compliant in deferasirox group), [i] *Two-Sample Kolmogorov-Smirnov Test* (abnormal distribution, serum ferritin level between compliant and non-compliant in deferasirox group), [j] *Mann-Whitney U test Test* (abnormal distribution, serum ferritin level between compliant and non-compliant in deferasirox group),

4. Discussion

This study reported that one-third of children had low transfusion regularity (non-compliance). This study reported that most children (55.7%) had a pre-transfusion hemoglobin of 7-8 g/dL. As many as 76.6% of children come for blood transfusions when hemoglobin has fallen to around 8.0 g/dL [17]. Research in Malaysia reported that 92.3% of children had hemoglobin levels below 9.0 g/dL [18]. In this study, most children compliant with blood transfusions will come with a hemoglobin level of 8-9 g/dL (55.4%). Hongally, et al. [19] reported that 52% of children had higher cut-off hemoglobin below 10.0 g/dL. Another study reported that 57.7% of patients had pre-transfusion Hb of less than 9.0 g/dL. Only 7.7% of children have pre-Hb between 9-10 mg/dL [18]. The mean hemoglobin level in children with thalassemia at our place is not above 9.0 g/dL. Although the management of thalassemia has evolved, clinicians often identify concerns about iron overload rather than anemia as the most crucial management problem [20]. Differences in the understanding of hemoglobin levels pre-transfusion and post-transfusion will cause delays in giving transfusions. Transfusion guidelines for thalassemia should identify these barriers and provide solutions for education to providers and patients.

The mean hemoglobin level in this study was 7.9 g/dL. Based on the [15], blood transfusions can be given to children with thalassemia if the hemoglobin level is less than 9 g/dL [8]. The mean pre-transfusion hemoglobin in Jamshedpur was 8.34 g/dL.[13)] In Punjab, it was 9.2 g/dL with a range of 4.2 g/dL to 11.6 g/dL [21]. In another study of 464 β-thalassemia patients in Egypt, the mean hemoglobin level was 5.7 g/dL (2.8-9.3 g/dL [22]. The difference in the mean pre-transfusion hemoglobin level can occur due to the policy of whether or not a different transfusion is required. Pretransfusion Hb values between 9-10 g/dL can prevent extramedullary hemopoiesis, suppress excess blood consumption, and reduce iron absorption from the digestive tract. Hemoglobin levels in this study were higher than reported in the literature [17, 19, 21, 22]. Our hospital has a policy of giving blood transfusions in

outpatient clinics if the hemoglobin level is above 7.0 g/dL. The parents preferred to bring their children earlier to prevent hospitalization before the hemoglobin level fell to 7.0 g/dL.

Previously, we used packed red cell (PRC) transfusion for all children with thalassemia and washed erythrocytes in the prehistory of severe allergic reactions. The leukoreduced PRC replaced the PRC several years ago. Leucodepleted packed red cells were unavailable in our institution due to limited insurance coverage. Prestorage filtration is strongly recommended by the Thalassemia International Federation (2021) if the blood bank pretransfusion filtration is acceptable and bedside filtration is only proper for alternative prestorage filtration [8]. A bedside filter leucodepletion of PRC was a better method in children with thalassemia. However, leukoreduction PRC using the buffy-coat method also effectively reduces transfusion reactions in resource-limited settings [23, 24]. Leukoreduction PRC in pediatric thalassemic patients also effectively prevented transfusion reactions in our institution.

Most children (56.2%) came every four weeks or more, especially those with good compliance to transfusions. As many as 29.2% of children get transfusions at least once every two weeks. The transfusion interval in Egypt is once every 1-6 weeks, averaging 4.41 weeks [22]. In Germany, transfusions intervale was at least once every three weeks [25]. Increasing age is related to the frequency of transfusions received each month. In children aged 0-5 years, most receive blood transfusions once a month, which increases to 2 times a month at 6-15 years old in Ahmedabad, India [26]. Blood transfusions every 2–4 weeks can maintain pretransfusion hemoglobin above 9.0–10.5 g/dL in children with thalassemia [8]. If the pre-transfusion Hb level in a child with thalassemia has reached 9-10 g/dL, transfusions are usually given monthly in infancy and after that at 2 to 4-week intervals in childhood until adolescence [27]. Older children generally require a greater volume of blood and transfusion requirements. Increasing age will increase the frequency of blood transfusions received per month. Increasing age will increase complications, the need for transfusion, and the worsening of the disease, so the need for blood transfusion will also increase. The interval between the two transfusion periods will determine the change in hemoglobin level after the transfusion. More frequent transfusions will cause discomfort and low compliance for the child and the parents. They also had lower hemoglobin levels and poor compliance.

The average need for blood transfusions for children with thalassemia is 236.77 ml/kg BW per year [21]. Pre-transfusion hemoglobin levels should be above 9.0 g/dL, and ferritin levels should be less than 3000 ng/mL [17]. Iron obtained from transfusions is 40 times (0.4 mg/kgBW/day) more than iron absorbed in the gastrointestinal tract (0.01 mg/kgBW/day) [16, 28]. The mean ferritin level in this study was 2285.2 ng/mL, with a range of 269.0 to 6268 ng/mL. Ferritin levels in this study were almost the same as other studies in India, namely 160.75-350 ng/mL to 6275-7594.0 ng/mL with an average of 2132.6-2683 ng/mL [17, 21]. The average ferritin level in older children is higher than in younger children, especially those with diabetes complications [22]. Low compliance would increase the risks of iron overload, heart failure, endocrine damage, liver cirrhosis, and growth failure [8]. On the other hand, low pre-transfusion hemoglobin levels may cause a poorer post-transfusion increment through enlargement of the spleen and extramedullary erythropoiesis [20].

The target serum ferritin value is between 500 and 1000 μg/L. Serum ferritin was measured every 1-3 months. The trends of ferritin are a more reliable indicator for adjusting therapeutic goals [8]. As many as 30% of patients had ferritin levels of less than 1000 ng/mL, but this study only reported 11.2% [22]. As many as 52.8% of children had ferritin levels of 1000-2500 ng/mL, slightly higher [22]. A previous study in our hospital reported 37.9% of TDTs children with ferritin levels less than 2500 ng/mL [7]. Our institution's policy for iron chelation is ferritin levels above 1000 ng/mL. The number and volume of transfusion do not determine when iron chelation begins. About 92.1% of children with thalassemia took iron chelation. Previous study reported iron chelation in 76.7% of children with beta-thalassemia after receiving more than 15 blood transfusions or serum ferritin above 1000 ng/mL [17]. Iron chelation therapy is essential to prevent complications related to iron overload in children with transfusion-dependent thalassemia [29]. The main iron chelator in this study was deferiprone in two-thirds of cases.

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This study did not evaluate factors related to the regularity and compliance of transfusion. The medical record must report body weight, pre-transfusion hemoglobin level, blood transfusion volume at each visit, and hemoglobin level before transfusion. We did not evaluate the demographic and psychosocial aspects of children and parents, availability of infrastructure, and knowledge. As many as 58% of 50 children with multi-transfusion thalassemia aged 5-10 years in Bangalore, India, come from low socioeconomic groups, predominantly rural areas. Most children also come when the hemoglobin is below 10.0 g/dL [19]. Adherence is a multidimensional phenomenon influenced by patient, treatment, and demographic factors. Factors related to patients include knowledge, patient education and caregivers, psychological factors, attitudes, beliefs, perceptions of disease severity, and expectations of treatment [30]. Compliance is the child's active and voluntary participation in managing the disease. Health workers, parents, families, and the surrounding environment can participate in disease management. Compliance may refer to behavior in complying with the provisions given by health workers. Further research needs to evaluate the factors that influence transfusion compliance.

5. Conclusion

Most children with TDTs have good transfusion compliance (69.7%). They come to the hospital for a transfusion before their hemoglobin level falls below 7.0 g/dL. Ferritin levels in children who were non-compliant with blood transfusion were higher than those with good transfusion compliance. Most non-compliant children with blood transfusion have ferritin levels above 2500 ng/dL.

Transparency: The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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Abbreviations:

Hb	: Hemoglobin
HPLC	: High Performance Liquid Chromatography
ELFA	: Enzyme-Linked Fluorescent Assay
MCV	: Mean Corpuscular Volume
NTDT	: Non Transfusion Dependent Thalassemia
PRC	: Packed Red Cell
TDTs	: Transfusion Dependent Thalassemia

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