Ocular Abnormalities in Correlation with Multi-transfused in Children with Beta Thalassemia Major

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Abstract: Thalassemia is the commonest haemoglobinopathies worldwide. Repeated blood transfusion lead to hemosiderosis which affects all the organ in the body including eyes. The aim of this study was to evaluate ocular abnormalities in children with beta thalassemia major who have received multiple blood transfusions. A cross-sectional study was conducted in the Thalassemia day-care centre of a tertiary care at H. Adam Malik Hospital Medan, Indonesia. Visual aquity, anterior segment, fundus, and retina were evaluated to screen ocular abnormalities. There were 37 patients with beta thalassemia major, male and female were 20 (51.3%) and 17 (48.7%), respectively, age 3 to 18 years. All patients received regular blood transfusions, but only 28 patients (78.4%) received iron chelation therapy. Opthalmologic examinations showed ocular abnormalities in 15 subjects (40.4%), cataract in 3 patients (8.1%), papil edema in 10 patients (27%), and papil atrophy in 2 patients (5.4%). Decreased visual acuity was observed in 8 patient (21.6%). Hyperpigmentation in bulbar conjunctiva were seen in 12 patients (32.4%). There was no significant correlation between ocular abnormalities and multiple transfusions. Regular ophthalmologic evaluations was needed to detect retinopathy and early changes in their ocular system for a better quality of life in thalassemic patients.

1 INTRODUCTION

Thalassemia is a severe genetic blood disorders caused by a mutation in the globin gene. Abnormal globin chains lead to the excessive destruction of red blood (Vichinsky EP, 2005). Beta thalassemia major is one of the most common hemoglobinopathy. Management of thalassemia major consist of regular blood transfusions therapy throughout the life, getting natural development and growth, reducing hyperplasia of erythroid tissue and deformities of skeleton (Cao A, 2010; Langhi D et al., 2016). Although transfusions can prevent death and decease mortality, iron accumulated from repeated blood transfusion and enhanced iron absorption by gastrointestinal tract can lead to organ damage such as heart, liver, endocrine gland, and skeletal system (Propper RD, 1980).

Mechanism of ocular manifestations in thalassemia is multifactorial such as regular blood transfusion therapy which causes iron overload. Iron chelating agents chelate other metals suchs as Copper, zinc, nickel, and cobalt essential for normal retinal function causing several ocular abnormalities. Deficiency micronutrients like zinc, vitamins like vitamin B_{12} can also lead to ocular manifestations. Iron deposition in eye can lead to several ocular abnormalities as a result of the disease itself or as side effects of iron chelators and include ocular surface disorders, cataract, angioid streak, retinal venous tortuosity, retinal pigment epithelium (RPE) degeneration and mottling, optic neuropathy, and decreased visual acuity (Taher A et al., 2006; Arden GB et al., 1984; Gartaganis S et al., 1989).

This study was conducted to assess the prevalence of ocular abnormalities in multi-transfused beta-thalassemia patients and to determine their relationship with serum ferritin level.

2 METHODS

A cross-sectional study was conducted in the Thalassemia day-care centre of a tertiary care H.

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Adam Malik Hospital Medan, Indonesia. Thirty seven children were included in this study. Inclusion criteria were children with beta thalassemia major with the age less than 18 years with regarding two years blood transfusion. Subjects have received packed red cell transfusions with a dosage of 15 ml/ Kg BW to maintain haemoglobin concentration after transfusion at levels greater than 11 g/dL for at least 2 years were enrolled in the study. Haemoglobin was measured before each transfusion and the serum ferritin levels was measured in all patients at 6-monthly intervals. The records were kept at the thalassemia day-care centre.

Ophthalmological assessment was assessed by Pediatric Ophthalmologist, included a detailed history of visual problems and visual aquity screening. Anterior segment was examined by using slit lamp and posterior segment screening was evaluated by using multimodal imaging in ophthalmology like indirect retinoscopy, optical coherence tomography (OCT) or fundus photo. Subjects who had history of corneal disease, using contact lens, ocular trauma, previous ocular surgery, and those taking topical medications were excluded in this study.

2.1 Statistical Analysis

The relationship between serum ferritin level and ocular abnormalities was analysed using Chi square test. Spearman test was used to determine the correlation between frequency and volume of transfusion with serum ferritin level. Statistical calculation was done using Statistical Package for Social Science (SPSS) version 24.0 at 95% confidence interval and P-value of <0.05 was considered as statistically significant.

3 RESULTS

There were thirty seven thalassemia subjects with the age 3–18 years were included in this study, there were 20 subjects (51.3%) were male and 17 subjects (48.7%) were female. Baseline characteristics of subjects were shown in **Table 1**. The dominant ethnic in this study was Javanese (59.8%). All subjects received regular blood transfusion, but only 28 patients (78.4%) received iron chelation therapy, and others (21.6%) without iron chelation treatments. Median age at diagnosis was 31.0 (3.0-180.0) months. Only 5 (13.5%) subjects had serum ferritin levels was less than 1000 ng/mL, and 32 subjects (86.5%) was more than 1000 ng/

Table 1. Baseline characteristics of subjects

	n (%)
Age, year	
<5	
5-10	
>10	
Gender	
Male	20 (51.3)
Female	17 (48.7)
Ethnicity	
Acehnese	2 (5.4)
Javanese	22 (59.8)
Karonese	3 (8)
Melayunese	2 (5.4)
Padangnese	6 (16)
Sundanese	1 (2.7)
Chinese	1 (2.7)

Table 1: Baseline characteristics of subjects

Mean body weight, kg (mean ±SD)	24.5 (8.8)
Mean body height, cm (mean ±SD)	123.6 (18.9)
Mean BMI, kg/m^2 (mean ±SD)	15.4 (2.2)
Median age at diagnosis, month (min-max)	31.0 (3.0-180.0)
Iron chelating agent Exjade Ferriprox None	 13 (35.1) 16 (43.3) 8 (21.6)
Serum ferritin level	
< 1000 ng/mL	5 (13.5)
1000-5000 ng/mL	20 (54.1)
5000-10000 ng/mL	8 (21.6)
>10.000 ng/mL	4 (10.8)
Median serum ferritin level, ng/mL ((Min – max)	2842.0 (430.8-31285.4)
Median transfusion volume, mL (min-max)	175.0 (10.0-525.0)
Median transfusion frequency, time (min-max)	12.0 (3.0-48.0)

Table 2: Ocular abnormalities findings

	n (%)
Characteristics of bulbar conjunctiva	
Normal	25 (67.6)
Hyperpigmentation	12 (32.4)
Characteristics of camera oculi anterior	
Normal	30 (81.1)
Hyperpigemtation	7 (18.9)
Visual acuity	
Normal	29 (78.4)
Decrease	8 (21.6)
Ocular abnormalities	
None	22 (59.5)
Papil edema	10 (27)
Complicated cataract	3 (8.1)
Papil atrophy	2 (5.4)

The association between serum ferritin levels and ocular abnormalities has been shown in **Table 3**. The prevalence of hyperpigmentation in bulbar conjunctiva and camera oculi anterior were 8 (66.7%) and 3 (42.9%), respectively, in subjects who had serum ferritin levels between 1000-5000 ng/ml. Visual acquity decreased in 8 (21.6%) in subjects, we also found 3 subjetcs with cataract, but there were no significant association between serum ferritin levels and hyperpigmentation, vivisual acquity, and cataract in our subjects.

Table 4 showed the correlation between frequency and volume of transfusion with serum ferritin level. There was significant association between blood volume of transfussion and serum ferritin levels (p<0. 05), but there was no significant association between frequency of transfussion with serum ferritin levels.

Table 3. Association between serum ferritin level and ocular abnormalities

Category of serum ferritin level	Bulbar conjunctiva				*p*
	Normal (%)	Hyperpigmentation (%)			
<1000	3 (12.0)	2 (16.7)			0.428
1000-5000	12 (48.0)	8 (66.7)			
5000-10000	6 (24.0)	2 (16.7)			
>10000	4 (16.0)	0 (0.0)			
	Camera oculi anterior				
	Normal (%)	Hyperpigmentation (%)			
<1000	4 (13.3)	1 (14.3)			0.920
1000-5000	17 (56.7)	3 (42.9)			
5000-10000	6 (20.0)	2 (28.6)			
>10000	3 (10.0)	1 (14.3)			
	Visual acuity				
	Normal (%)	Decreased (%)			
<1000	3 (10.3)	2 (25.0)			0.283
1000-5000	17 (58.6)	3 (37.5)			
5000-10000	5 (17.2)	3 (37.5)			
>10000	4 (13.8)	0 (0.0)			
	Ocular abnormalities				
	None (%)	Oedema of papilla (%)	Complicated cataract (%)	Atrophy of papilla (%)	
<1000	3 (10.3)	2 (25.0)	0 (0.0)	0 (0.0)	0.632
1000-5000	17(58.6)	3 (37.5)	1 (33.3)	2 (100.0)	
5000-10000	5 (17.2)	3 (37.5)	1 (33.3)	2 (100.0)	
>10000	4 (13.8)	0 (0.0)	1 (33.3)	0 (0.0)	
	Ocular abnormalities				
	Complicated cataract (%)		No cataract (%)		
<1000	0 (0.0)		1 (8.3)		0.541
1000-5000	1 (33.3)		8 (66.7)		
5000-10000	1 (33.3)		2 (16.7)		
>10000	1 (33.3)		2 (16.7)		

*Chi square test

Table 4. Correlation between frequency and volume of transfusion with serum ferritin level

	Mean	r	*p*
Frequency of transfusion, time	17.6	0.199	0.239
Serum ferritin level, ng/mL	5033.2		
Volume of blood transfusion, mL	188.7	0.544	<0.001
Serum ferritin level, ng/mL	5033.2		

*Spearman test

4 DISCUSSION

Thalassemic patients are on lifelong blood transfusion therapy. Multiple or repeated blood transfusions lead to siderosis and adverse ocular changes may occur as a result of the disease or due to iron overload and chelation therapy. Adverse retinal effects may occur as a result of the iron chelators or the disease itself and include the following: Retinal pigment epithelium (RPE) degeneration, RPE mottling, retinal venous tortuosity and vitrretinal hemorrhages. Thalassemic patients may present with decresed visual acuity, color vision anomalies, hyperpigmentasi, papil edema, papil athrophy, thinning and tortuosity of retinal vessels, vitreo-retinal hemorrhages, night blindness, cataracts, visual field defect and optic neuropathy. Thalassemia major may also be associated with a nonproliferative pigmentary retinopathy due to liberation of free iron as a result of hemolysis (Gartaganis S et al., 1989; Wong RW et al., 2001).

This study was conducted to detect various ocular changes in patients who were on regular transfusion and iron chelating agent. We evaluated 37 thalasemic children with ocular abnormalities in 15 patients (40.5%), such as visual acquity decreased in 8 patients (21.6%). There was no significant correlation between serum ferritin levels and edema and athropy papil, and cataract. Other studies reported ocular abnormalities were found in 41.3%, 36%, and 38% (Gartaganis S et al., 1989; Dewan P et al.2011; Soecinelli R et al., 1990). Difference results of ocular abnormalities that had been reported in previous studies may be due to differences in parameters used to evaluate ocular abnormalities, it is difficult to make an accurate comparison. Ocular changes were seen more in children above 10 years of age and was less in children below 5 years of age. This clearly shows that longer the duration of the illness more are the eye changes.

Decreased visual aquity was observed in 8 patients (21.6%), this result was almost same with other studies that reported the insidence of decreased visual acquity was about 15.5–30% in thalassemic patients (Taher A et al., 2006; Gartaganis S et al., 1989). The presence of ocular abnormalities was correlated with serum ferrin levels and multiple transfusion. This study reported ocular abnormalities were found in 16 (84%) subjects with the serum ferritin levels were more than 1000, and less than 1000 ng/mL in 3 subjects (16%). Iron causes oxidative damage to protein, lipids, and DNA through the generation of free radicals in the Fenton reaction and it has been shown to disrupt the blood-retinal barrier. Iron may play a role in the pathogenesis of retinal degeneration as a source of free radical damage. Iron toxicity from multiple blood transfusions may contribute to beta-thalassemia retinopathy. Iron is important component of many metabolic processes, but appropriate regulation is necessary to prevent toxicity (Liaska A et al., 2016; Song D et al., 2013).
The limitations in our study were that very few children with thalassemia use iron chelating therapy due to low their low socio-economic level, and we could not evaluate the effect of chelation therapy on the ocular abnormality especially on the retina in thalassemic children. We did not correlate the ocular abnormalities with frequency and volume of blood transfusion in our subjects. Our study has same limitations, we did not compare the ocular abnormalities with frequency and volume blood transfusion therapy for thalassemic patients, differences between iron chelation regimen and there is a possibility that their ocular abnormalities could have occurred before first time blood transfusion treatment. Overall, the correlation between ocular abnormality and frequency and volume blood transfusion has not been established in present study, hence, further prospective investigations with a large sample of thalassemia patients are suggested.

5 CONCLUSION

The ocular abnormalities in our subjects were asymptomatic, but 15 subjects (40.4%) was revealed ocular abnormalities. We did not find any significant correlation between ocular abnormalities with serum ferritin levels and multiple transfusion, but a significant association was found between volume of blood transfussion and serum ferritin levels. Since life expectancy in patients with beta thalassemia major increases, it is necessary to screen for ocular abnormalities in all children with thalassemia to improve the quality of life of thalassemic patients.

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

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