CORRELATIONS BETWEEN ORAL IRON CHELATION THERAPY ADHERENCES WITH THALASSEMIA CHILDREN'S GROWTH IN ANNA MEDIKA HOSPITAL

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ABSTRACT

Background: *Thalassemia is an inherited blood disorder in which the body makes an abnormal form of haemoglobin. Thalassemia in children not only causes psychosocial problems, but also physical problems, one of that problem is growth. This study aims to determine the correlation between oral chelation therapy adherences with thalassemia children's growth in Anna Medika Hospital.*

Methods: *The method of this research is retrospective. The subjects of this study consisted of 64 thalassemia major patients obtained by quota sampling technique in September-October 2017. The instruments of this research are a medical record, MMAS questionnaire for compliance of medical treatment (Morisky Medication Adherence Scales) and assessment of children's growth was measured by using the Z Score IMT/U.*

Result: *The analysis of results with Chi-Square test (α=0.05) show that p value=0.021 (p<α) OR=3.400, so it can be concluded that there is a correlation between oral chelation therapy adherence and thalassemia children's growth.*

Conclusion: *Based on the result of research there is a correlation between oral chelation therapy adherence and thalassemia children's growth.*

Keywords: *Thalassemia, Children's Growth, Oral Chelation Therapy, Compliance with Medical Treatment*

INTRODUCTION

Thalassemia is an inherited blood disorder in which the body makes an abnormal form of haemoglobin. Haemoglobin is a protein that is rich in Ferrum substance in the red blood cells to transport oxygen from the lungs to all parts of the body [(1,28)]. Molecularly, thalassemia is distinguished from alpha (α) and beta (β), whereas clinically, it is differentiated in minor and major thalassemia. [2, 27].

Thalassemia is the most common hereditary blood disorder in the world. About 7% of the world's population is abnormal gene carriers and more than half a million children with major β thalassemia are born annually [(3, 30)]. In some areas of Southeast Asia, up to 40% of the population has one or more thalassemia genes. According to Basic Health Research in 2007, the national prevalence of thalassemia was 0.1%, with 8 provinces showing prevalence above the national prevalence of Nanggroe Aceh Darussalam (1.34%), DKI Jakarta (1.23%), South Sumatra (0.54%), Gorontalo (0.31%), Riau Island (0.3%), West Nusa Tenggara (0.26%), West Papua (0.22%) and Maluku (0.19%) [4]. While in 2011, it was reported by Thalassemia Foundation Indonesia-Parent Association of Thalassemia Patients (YTI-POPTI) that West Java Province has the highest number of thalassemia sufferers in Indonesia as much as 35% [5].

Thalassemia in children does not only cause psychosocial problems, but also physical problems like growth [24]. Factors that affect the growth of thalassemia children are genetics and environment. Ferritin and haemoglobin levels should be maintained at approximately 10 g/dl with the prevention of hemochromatosis to avoid growth disorders [6]. To maintain haemoglobin levels, thalassemia sufferers need regular blood transfusions. However, a continuous blood transfusion can increase the accumulation of Ferrum substance in the body causing Ferrum deposits in the liver, endocrine and heart tissues [7].

A therapy that can be used to bind excess of Ferrum substance in the body is iron chelation. In Indonesia, there are two types of iron chelation treatments; desferoxamine parenterally and deferiprone and oral deferasirox [8]. However, the most common therapy used is an oral iron chelation therapy. It is an alternative for thalassemia patients who can not consume deferoxamine (DFO) due to allergies, toxicity, discomfort in the use of DFO, unavailability of DFO, and higher cost [9, 25, 26]. Based on Safitri research et. al (2015) in Riau, there is a significant correlation between adherence to oral iron chelation consumption with growth due to a reduction of Ferrum deposit in children with thalassemia. Auda in Safitri et. al (2015) explains that rational oral iron chelation therapy has a smaller risk of impaired growth compared with the irrational [(10)]. Moreover, according to Trachtenberg et al. al (2011) age and adverse effects of iron chelation can affect patient compliance rates in consuming iron chelation[(11)]. In line with Thavorncharoensap et. al (2010) who reported that the age and quality of life of thalassemia children, one of which was assessed from physical health including height and weight of children had a significant relationship [12]. However, Ejaz et. al (2015) stated that the Adverse Effects due to oral iron chelation therapy did not affect the growth of thalassemia children[(13)]. Therefore, this study was conducted to determine the relationship of adherence to oral iron chelation with the growth of children with thalassemia.

METHOD

The type of research used is non-experimental with qualitative descriptive design and retrospective retrieval data. The sampling technique used is non-probability with purposive sampling. This research was conducted at Thalassemia Unit of Anna Medika Hospital of Bekasi in September-October 2017. The populations in this study were all major thalassemia patients who received oral iron

chelation therapy at Anna Medika Hospital in Bekasi in September-October 2017. The samples in this study were 64 major thalassemia patients in accordance with inclusion and exclusion criteria divided into 2 groups; 32 thalassemia major patients with good growth and 32 major thalassemia major patients with poor growth. The inclusion criteria in this study were children with thalassemia major at 6-12 years old who received oral iron chelation therapy at least 1 year and their parents are willing to be interviewed. The exclusion criteria are children with thalassemia major at 6-12 years old who undergo oral iron chelation therapy but accompanied by other comorbidities consuming drugs such as rifampicin, phenobarbital, phenytoin and antacids. Data were collected using medical records, MMAS (Morisky Medication Adherence Scales) questionnaire and measurement of child growth with Z Score on IMT/U. The data analysis used univariate analysis to know the description of patient characteristics, drug consumption, drug Adverse Effects and drug adherence. Meanwhile, for bivariate analysis of drug compliance factor, ferritin level, drug side effect, therapy rationality and age used chi-square and t-test analysis.

RESULTS AND DISCUSSION

Characteristics of Patients Children Thalassemia Major

This study described characteristics based on age, sex, child weight, the height of child and duration of illness. Distribution of patient characteristics can be seen in Table 1. Patients with thalassemia often occur in primary school children aged 6-12 years with the lowest age of 6 years and the highest age is 12 years. In this study, patients with thalassemia mostly occurred at age 10 years (20.3%) with the number of major thalassemia patients more common in men (57.8%) than women (42.2%) according to Safitri research 2015) which states that the majority of respondents of children with thalassemia are male [10]. The results showed that thalassemia patients' weight was in the 20-30 kg range of 51.6% and children with weight ≥30 kg had the lowest frequency with a percentage of 7.8%. The height of patients with thalassemia children is found to be ≤123 cm (57.8%). The majority of children with thalassemia have growth disorders. They grow abnormally so that the nutritional status of children with thalassemia is very important to be noted. Long-terms of children thalassemia sufferers were divided into 2 categories: short (≤5 years) and long (> 5 years). Based on this study, thalassemia children with the long category is 53.1% and short category of 46.9%.

Table 1. Characteristics of Pediatric Thalassemia Children

Characteristics	Frequency (n)	Percentage (%)
Age		
6 years	7	10,9
7 years	7	10,9
8 years	12	18,8
9 years	9	14,1
10 years	13	20,3
11 years	8	12,5
12 years	8	12,5
Gender		
Female	27	42,2
Male	37	57,8
Weight		
≤ 19 kg	26	40,6
20-30 kg	33	51,6
≥ 30 kg	5	7,8
Height		
≤ 123 cm	37	57,8
≥ 123 cm	27	42,2
Long-term of sickness		
Short	30	46,9
Long	34	53,1

Overview of Drug Use in Pediatric Thalassemia Children

Description of the use of drugs is an illustration to find out the iron chelation drug used and the dosage of drugs that can be seen in Table 2. The results showed that the most commonly used oral iron chelation therapy is Ferriprox (82.8%) while Exjade (17.2%). The standard dose used in this study for Ferriprox is 75 mg/kg/day, while Exjade 30 mg/kg /day. In this study, the dose of the drug divided into 2 categories namely the dose achieved and unachieved one according to the existing standard doses. From Table 2 below, it was found that pediatric thalassemia patients who achieved standardized doses were 48.4% and patients with thalassemia did not achieve the desired dose were 51.6%.

Adverse Effects of Drugs on Pediatric Thalassemia Patients

Description of drug adverse effects in children patients with thalassemia is an illustration to determine the adverse effects of drugs, the types of adverse effects drug that arises and the type of follow-up in the event of adverse effects can be seen

in Table 3. The results of this study state that children patients with thalassemia who are undergoing oral iron chelation therapy more do not feel the adverse effects of 53.1%, while those who feel the adverse effects of 46.9%. There are various adverse effects of medication perceived by thalassemia children; vomiting (9,4%), joint pain (12,5%), headache (6,2%), diarrhoea (1,6%), redness of skin (6.2%) and neutropenia (10.9%). adverse effects arising above will disappear by itself without having to reduce the dose or stop the treatment of iron chelation [14]. The results also indicate that the parents of patients who continued oral iron chelation therapy were 87.5% and those who did not continue as much as 12.5%.

Table 2. Overview of Drug Use in Pediatric Thalassemia Patients

Information	Frequency (n)	Percentage (%)
Medicine name		
Ferriprox	53	82,8
Exjade	11	17,2
Dosage of medication		
Achieved	31	48,4
Not achieved	33	51,6

Table 3. Adverse Effects of Drugs On Pediatric Thalassemia Patients

Information	Frequency (n)	Percentage (%)
Adverse Effects		
Absence	33	51,6
Presence	31	48,4
Types of Adverse Effects		
Gag	6	9,4
Joint pain	8	12,5
Headache	4	6,2
Diarrhea	1	1,6
Redness of the skin	4	6,2
Neutropenia	7	10,9
Type of follow-up		
Continue	56	87,5
Discontinue	8	12,5

Table 4. Description of Compliance of Oral Iron Chocolate Compliance in Pediatric Thalassemia Children

adherence	Frequency (n)	Percentage (%)
High compliance	35	54,7
Low compliance	29	45,3

Descriptions of Compliance of Oral Iron Chelation on Patients of Thalassemia Children

The description of adherence to oral iron chelation consumption in thalassemia children can be seen in Table 4. Compliance of oral iron chelation consumption is divided into 2 categories: low adherence with score> 2 and high adherence with score 1-2 based on MMAS questionnaire. The results of this study found that patients with thalassemia children with high adherence were 54.7% and patients with low-compliance thalassemia children were 45.3%.

Compliance Relation of oral iron chelation to Child Growth

The association of adherence of oral iron chelation to the growth of children was assessed by bivariate analysis using chi-square test. The result of the analysis of the correlations between adherence of oral iron chelation consumption and the growth of thalassemia children found that there were as many as 24 (61.5%) with high adherence and growing well, while there were 8 (32%) with low adherence and growing well. The result of chi-square statistic test obtained p-value = 0,021 (≤0,05) which shows there is difference of proportion of growing incidence of thalassemia children between low and high adherence (there is a significant correlation between adherence to oral iron chelating adherence to child growth) and also obtained OR amounting to 3,400, meaning that thalassemia children patients with high oral iron chelation drug adherence have a 3.400 times chance to grow well compared with thalassemia children with low oral iron chelation adherence. This is in accordance with the results of Safitri research (2015) which says that there is a significant relationship between adherence to the growth of thalassemia children [10, 20, 23]. Provision of an optimal oral iron chelation can reduce Ferrum deposits that occur in children with thalassemia [17]. When a thalassemia patient does not get an oral iron chelation, there will be progressive liver dysfunction

in the liver, heart, and endocrine gland resulting in liver fibrosis, liver cirrhosis, heart failure, diabetes mellitus, hypogonadism, hypothyroidism, hypoparathyroidism to death [15, 16].

Table 5. Compliance Relation of Oral Iron Chelation to Child Growth

Obedience	Growth				Total		OR (95% CI)	P Value
	Good		Bad					
	N	%	N	%	N	%		
High	24	61,5	15	38,5	39	100	3,400 (1,179-9,808)	0.021
Low	8	32	17	68	25	100		
Total	32	50	32	50	64	100		

Table 6. Relationship of Ferritin Contents to Child Growth

Ferritin levels	Growth				Total		OR (95% CI)	P Value
	Good		Bad					
	N	%	N	%	N	%		
< 3000 ng/L	22	64,7	12	35,3	34	100	3,667 (1,303-10,321)	0,012
≥ 3000 ng/L	10	33,3	20	66,7	30	100		
Total	32	50	32	50	64	100		

The Relationship of Ferritin Contents to Child Growth

The result of analysis of the correlation between ferritin level to the growth of thalassemia children showed that there were 22 (64,7%) thalassemia children with ferritin <3000 ng / L with good growth, while there were 10 (33,3%) thalassemia children with ferritin ≥3000 ng / L with good growth. The result of chi-square statistic test obtained p-value = 0,012 (≤0,05) so it can be concluded that there is a difference of proportion of growth incidence both between ferritin <3000 ng / L and ferritin ≥3000 ng / L (there is a significant relationship between ferritin to child growth). In addition, the results of the analysis also obtained OR = 3,667, meaning that thalassemia children with ferritin levels <3000 ng / L has a 3.667 times chance to grow better than patients with thalassemia with ferritin levels ≥3000 ng / L. This is consistent with the research of Made and Ketut (2011) which states that serum ferritin levels have a direct relationship with the rate of growth disorders in thalassemia patients [18, 29]. Other studies have also mentioned that ferritin levels greater than 3000 ng / L can affect the growth of thalassemia children [6, 19].

The Relationship of Adverse Effects on Child Growth

The result of analysis of the correlation between side effect and growth of thalassemia children was obtained that 15 (44,1%) there was no side effect with good growth and 17 (56,7%) there was a side effect with good growth. In the statistical test results obtained p = 0.316 (> 0,05) which can be concluded, there is no difference in the proportion of growing incidence of children with the presence or absence of adverse effects of iron chelation drug. From the results of analysis also obtained value OR = 0.604. This is in accordance with Ejaz et. al (2015) who stated that the adverse effects due to oral iron chelation therapy did not affect the growth of thalassemia children [13]. Adverse Effects arising from the use of oral iron chelation are temporary and will disappear on their own without interrupting the iron chelation treatment underway [21].

Age Relation to Child Growth

The average age with good growth was 9.44 with a standard deviation of 1.585, while the mean age with poor growth was 8.75 with a standard deviation of 2.079. The result of the statistical test of t-test was obtained p-value = 0.142 (> 0,05) meaning that at alpha 5% there was no significant difference of mean age between thalassemia children patients with good and bad growth. This is not in accordance with Thavorncharoensap et. al (2010) who reported that the age and quality of life of thalassemia children, one of which was assessed from physical health including height and weight of the child had a significant relationship [12].

Table 7. Relationship Adverse Effects on Child Growth

Adverse Effects	Growth				Total		OR (95% CI)	P Value
	Good		Bad					
	N	%	N	%	N	%		
Absence	15	44,1	19	55,9	34	100	0,604 (0,224-1,624)	0,316
Presence	17	56,7	13	43,3	30	100		
Total	32	50	32	50	64	100		

Table 8. Aged Relationship to Child Growth

Growth	Mean	SD	SE	P *Value*	N
Good	9,44	1,585	0,280	0,142	32
Bad	8,75	2,079	0,368		32

Table 9. Relationship of Therapeutic Rationality to Child Growth

Therapeutic Rationality	Growth				Total		OR (95% CI)	P *Value*
	Good		Bad					
	N	%	N	%	N	%		
Rational	23	63,9	13	36,1	36	100	3,735 (1,314-10,618)	0,012
Irrational	9	32,1	19	67,9	28	100		
Total	32	50	32	50	64	100		

Relationship of Rationality of Therapy to the Growth of Children

The result of analysis of the correlation between the rationality of therapy with the growth of thalassemia children showed that there were 23 (63,9%) get rational therapy with good growth and there were 9 (32,1%) get irrational therapy with good growth. In result of chi-square statistic test obtained p-value = 0,012 (≤0,05) can be concluded, there is a significant correlation between rationality therapy with the growth of thalassemia children. From the analysis results obtained OR value = 3.735, meaning thalassemia patients who get therapy in a rational opportunity 3.735 times can grow better than those who get therapy in irrational. This is in accordance with Auda's statement in Safitri (2015) which states that the rationality of therapy is very important to avoid the occurrence of growth disorders in thalassemia children sufferers [(10)]. The therapeutic rationality in this study was assessed from appropriate drug selection, a precise indication of disease, precise follow-up, precise information, precise dosage, and precise assessment of the patient's condition [22].

CONCLUSIONS AND RECOMMENDATIONS

Based on the result of chi-square analysis with 95% confidence level and significance value, α = 0,05 obtained by value p <α so that Ho is rejected which mean there is a significant correlation between adherence of oral iron chelation adherence to children growth with thalassemia. In addition, the levels of ferritin and rationality of therapy also have a significant relationship with the growth of children with thalassemia.

Suggestions for the next researcher are

a. Future researchers are advised to investigate further about other factors that affect the growth of children with thalassemia.
b Researchers are advised to conduct research on some hospitals to obtain more valid data.

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BIBLIOGRAPHY

1. *McPhee, S.J, & Ganong, W.F., 2010, Pathophysiology of disease Edition 5, Jakarta: EGC*
2. *Mehta A, Hoffbrand A V., 2008, Interpreting: Hartanto H, Hematology at a Glance, Erlangga, Jakarta*
3. *Hastuti, Retno Puji, 2015, Factor Analysis related to Parenting Anxiety Level of Children with Thalassemia in Ahmad Yani Hospital, Metro Health Journal Sai Wawai Vol VIII No. 2, 49-54*
4. *Ministry of Health RI, 2007, Basic Health Research 2007, Agency for Health Research and Development of the Ministry of Health of the Republic of Indonesia, Jakarta*
5. *Thalassemia Foundation Indonesia-Association of Parents of Thalassemia Patients (YTI-POPTI), 2011, West Java Ranking 1 thalassemia sufferers, retrieved from http://web.rshs.or.id/jawa-barat-ranking-1-penderita- thalassemia /, October 21, 2017.*
6. Andayani, S.H., Sekarwana, N., & Fadil, R. 2008. *Association between age and serum ferritin level with bone age deficit in children with thalassemia major*. Paediatrica Indonesiana Vol 48 No 1. 33-36
7. *Rudolph, A. M., Hoffmand, J. I. E., & Rudolph, C. D., 2007, Pediatric textbook. (Samik, W. & Sugiarto, Translator). EGC, Jakarta*
8. *Thallasemias International Federation (TIF), 2012, Emergency Management of Thalassemia, Available online: http://www.thalassaemia.org.cy, 9 October 2016*

9. The Aplastic Anemia and MDS International Foundation, 2016, *Iron Chelation*, http://www.aamds.org/treatments/therapies/iron-chelation, 15 Februari 2017
10. *Safitri R., Ernawaty J., Karim D., 2015, Compliance Relationship Transfusion and Iron Chelation Consumption Against Child Growth Thalasemia, JOM Vol 2 No. 2, Riau*
11. *Trachtenberg F., Vichinksy E., et. al., 2011, Iron chelation adherence to deferoxamine and deferasirox in thalassemia, Retrieved from http://onlinelibrary.wiley.com/doi/10.1002/ajh.21993/full, October 21, 2017*
12. Thavorncharoensap M., Torcharus K., Nuchaprayoon I., Riewapaiboon A., Indaratna K., Ubol B., 2010, *Factors affecting health-related quality of life in Thai children with thalasemia*, https://www.ncbi.nlm.nih.gov/pubmed/20180983, 25 Februari 2017
13. *Ejaz, MS, Baloch S., Arif, H., 2015, Efficacy and Adverse Effects of Oral Chelating Therapy (Deferasirox) in Multi-Transfused Pakistani Children with B-Thalassemia Major, Retrieved from https: //www.ncbi. nlm.nih.gov/pmc/articles/PMC4485283/, October 6, 2017*
14. *Thalassemia International Federation (TIF), 2008, Guidelines for the Clinical Management of Thalassemia, Available online: http://www.thalassaemia.org.cy, October 14, 2016*
15. *Yaish, Hassan M., 2017, Pediatric Thalassemia Treatment and Management, Retrieved from https://www.emedicine.medscape.com/article/958850-treatment#d6, 5 October 2017*
16. *Gatot, D., et al, 2007, The latest approach to iron chelation in thalassemia. Sari Pediatri, Vol. 8, No. 4, 78-84*
17. Kwiatkowski J.L., Cohen A.R., 2004, *Iron chelation therapy in sickle-cell disease and other transfusion-dependent anemias*. Hematol Oncol Clin N Am
18. *Made, A., Ketut, A., 2011, Growth Profile, Pre-Transfusion Hemoglobin, Ferritin Level, and Child Bone Age in Major Thalassemia. Sari Pediatri Vol. 13 No. 4*
19. Pots, N.L. & Mandleco, B.L. 2007. *Pediatric Nursing; Caring for children and their families* (2nd ed), Thomson Corporation, New York
20. Osterberg, L., Blaschke, T., 2005. *Adherence to Medication*. http://www.ub.edu/farmaciaclinica/projectes/webquest/WQ1/docs/osterberg.pdf. 19 April 2017
21. *Eleftheriou, Androulla, 2011, Thalassemia International Federation (TIF): All About Thalassemia, Available online: http://www.thalassaemia.org.cy, October 14, 2016*
22. *Ministry of Health RI, 2011, Module on Rational Drug Use, Ministry of Health RI, Jakarta*
23. Zullig, Leah L., Bosworth Hayden, 2017, Engaging Patients To Optimize Medication Adherence, Durham Veterans Affairs Medical Centre
24. *Sari, Teny Tjitra, 2016, Thalassemia, National Seminar on Pharmaceutical "Save, Friendly & Be A Hero For Thalasemia", Jakarta*
25. Old, J., 2013, *Hemoglobinopathies and Thalassemias*, In: Rimoin, D.L., Pyeritz, R.E., Korf, I. Emery and Rimoin's Essential Medical Genetics. Elsevier.
26. *Eleftheriou, Androulla, 2007, Thalassemia International Federation (TIF): About Thalassemia, Available online: http://www.thalassaemia.org.cy, October 25, 2016*
27. Cohen, A.R., Galanello, R., Pennel, D.J., Cunningham, M.J.,Vichinsky, E., 2004, *Thalassemia*, Hematology
28. *Honig, G.R., 2000, Hemoglobin Disorder, In Behrman R.E, Kliegman R., Arvin A.M. 2000, Nelson Child Health Science Volume 2 Issue 15, EGC, Jakarta*
29. *Chamidah, Atien Nur, 2009, Early detection of growth disorders and child development, journal.uny.ac.id/index.php/jpk/article/download/789/613, February 12, 2017*
30. Shaligram D, Girimaji S.C, Chaturvedi, 2007, *Pyschological problems and quality of Life children with thalassemia*, Indian Journal of Pediatrics