CLINICAL MANIFESTATIONS OF CHILDREN WITH THALASSEMIA MAJOR: CLINICAL COURSE ONE YEAR LATER

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ABSTRACT

Background: Thalassemia major is a genetic blood disorder which required a lifelong transfusion dependent. The purpose of this study is to evaluate the clinical course of newly diagnosed thalassemia major patient in one year later when post diagnosis was done.

Method: It is a cross–sectional study by using descriptive quantitative method. The secondary data of medical record was collected from Outpatient Medical Record Installation Dr. Hasan Sadikin General Hospital Bandung which started from September to November 2016. The data of 47 subjects from 408 thalassemia being recruited. The inclusive criteria of subjects who are the newly diagnosed thalassemia major patient visited from 1 October 2013 to 30 September 2016. The clinical course was evaluated at one year later which consist of transfusion intervals, pre–haemoglobin level, spleen size, weight–for–age <-2 SD (z-score), ferritin level and iron chelation therapy demand. The result were analyzed using SPSS (statistic software) for the descriptive statistics.

Result: Out of the 47 thalassemia subjects, most them were male with 31 (66%) subjects and female with 16 (44%) subjects. All patients had received first transfusion when diagnosis established at 12 months. The clinical course of newly diagnosed talasemia major in one year later revealed the patients need regular transfusion every 4–5 weeks, mean pre–haemoglobin level at 7.5±1 g/dl, there were about 85.1% patients have a spleen size less than 3 cm, weight–for–age were improved when there were only 48.9 % was <–2 SD (z-score), and mean ferritin level was 1132.4±1037.5 ng/dl. About 97% of patients received iron chelation therapy as their ferritin value >1000 ng/dl after received one year transfusion.

Conclusion: All of the newly diagnosed thalassemia major at one year later were thalassemia dependent transfusion (TDT) major patients with ferritin level that keep up increasing.

Keywords: Blood transfusion, clinical course, thalassemia major, thalassemia dependent transfusion (TDT).

INTRODUCTION

Thalassemia are a group of genetic disorders which commonly found in many tropical and subtropical areas.[1] Geographical distribution of thalassemia is now worldwide not only particularly restricted in Mediterranean. This major public health problem encountered in some 60 countries including Italy, Greece, parts of North and West Africa, the Middle East, the Indian subcontinent, Southern Far East and South-East Asia that together comprising known as "Thalassemia Belt".[2,3] Due to global migration, Indonesia country were not exceptional. It accounts over 50% of cases of severe beta thalassemia in Indonesia.[4]

In Indonesia, the data from Badan Pusat Statistik (2015) was reported that the total citizen estimated around 254,9 million altogether and about 7,700 peoples are suffering thalassemia.[5,6] World Health Organization (WHO) also mentioned the thalassemia carrier in Indonesia is about 6-10% in which every 100 normal individuals, there are 6-10 peoples were identified as a carrier.[7] Meanwhile, West Java province have been marked as the highest prevalence with thalassemia disease in Indonesia.[6]

There is still not found the most successful ways for completely healing the thalassemia. Thalassemia major need combination of regular blood transfusion and iron chelation therapy for their whole life in order to survive. Patient also need some complement medicines such as folic acid, calcium, vitamin K and many other medicines depends on patient condition.[8] If the children are not being transfused, they will die before the age of 6 years old. In addition, if the child are being transfused but not chelated, they die before the age of 20 (Agouzal et al, April 2010). Therefore, fatal cases was a reality happened in genetic blood disorder.[9]

Transfusion is a lifesaver but variety of complication may occurred. Risks of frequent blood transfusion may enhance the hepatotoxicity due to iron overload caused by hemoglobin destruction. Excess storage of iron informed of ferritin is very harmful that can effected the systemic body system and organ dysfunction such as skin, cardiovascular and liver disease, pancreas problem, spleen, behave and neurotic problems.[3] Endocrinopaties from iron overload associated with growth failure or retardation, gonadal dysfunction and delayed puberty. On the other hand, transfusion related infection may existed. The symptomatic clinical features such as pallor and anemia, jaundice, hepatosplenomegaly, growth problem and bone deformities among this children may influenced their quality of life.

Thalassemia major results from decrease biosynthesis of both alpha or beta globin chains of hemoglobin. The clinical course of thalassemia was influenced by genetic interaction which based on the type of mutation. The environmental factor was included such as the compliance towards optimum management of thalassemia. The objective addressed by this work is to describe the clinical course of newly diagnosed thalassemia major patient in one year later when post diagnosis have been done. One year of blood transfusion is very useful as early therapy evaluation so that an appropriate management can be made to improve their survival rate and quality of life.

LITERATURE

Thalassemia refers to inherited blood disorders in globin chain production in which presence of gene mutations that reduce the synthesis of α globin or β globin chains. It created the imbalance haemoglobin. The presence of disturbance in the quantity of globin production of haemoglobin is the prove for primary pathology causes in thalassemia.

The lifespan of abnormal red blood cell in thalassemia is less than 120 days. In thalassemia, the red blood cell easily to be broken down causes anemia to be formed in which decrease oxygen carrier capacity. When the bloodstream is lack with oxygen throughout body,the clinical features such as pale or anemic, fatigue, slow growth and other health problems may be noticed.

There are numerous type of thalassemia either the defects in alpha or beta thalassemia. In the β-thalassemia in which can be either major, intermedia or minor. For alpha thalassemia, it consist α-chains are encoded by two α -globin genes, which located on chromosome. While

the β-thalassemia, it consist of β chains are encoded by a single β-globin gene located on chromosome 16. For each clinical syndrome, it can be classified into more specific part.

The clinical features in thalassemia happen when lack of oxygen flow in the blood because not enough production of haemoglobin. The infant with β-thalasemia major usually can be seen within the first year of life and early childhood with pallor, failure to thrive, variable degree of jaundice, looks weakness and fatigue, recurrent infection, abdominal enlargement due hepatosplenomegaly and slow growth during puberty. This is the most common features that can be observed from physical findings. The children's haemoglobin level is about 4-8 g/dL. If the infant was inadequately transfuse blood, it may lead to severe chronic anemia and stimulate the more stronger erythropoiesis. This severe anemia causes the expansion of bone marrow space and characteristic skeletal changes of the skull, hand bones, and long bones. The Mongoloid facies is the result from the marrow expansion of facial bones with hyperthrophy of the maxilla causing forward protruding of the upper teeth and overbite, a sunken nose, widely space eyes, and prominent cheek bones. While based on skull radiographs, the widening of the diploid space and radiating striations giving the typical "hair-on-end".

The diagnosis can be confirmed based on clinical presentation and laboratory test. Based on clinical features, there are presence of anemia usually with the mean value of haemoglobin approximately 8 g/dL, hepatosplenomegaly, jaundice, changes in facial bone and existence of growth retardation. There must also have history of β-thalasemia trait in both parents or any history of frequent blood transfusion. For diagnosis based on the laboratory test, performed the complete blood count and there are some other hematological tests for example peripheral blood film and haemoglobin electrophoresis.

The transfusion is given for the first time according to the condition of haemoglobin level. The first condition is when the haemoglobin is less than 7 g/dL that had been examined for two times occasion for two weeks apart. While the other condition is when the haemoglobin value is more than 7 g/dL that accompany with clinical features such as abnormal facial changes, impaired body development, para-spinal masses, severe bone changes and enlarging liver and spleen. The targets of transfusion is to maintain the pre transfusion haemoglobin level at about 9.5 g/dl until 10.5 g/dl. After the transfusion had been given, it must keep the mean of post-transfusion haemoglobin at 13.5 g/dl until 15.5 g/dl. In addition, need to remember to keep the mean of haemoglobin value at 12 g/dl until 12.5 g/dl. All of these value target is very important in order to reduce the sign of anemic and allow normal physical activity and growth for these children. Transfusion interval may varies from each patient usually at 4 weekly interval as rate of haemoglobin decline is at 1 g/dl/week.

The iron chelation therapy such as desferrioxamine, deferiprone or deferasirox need to be given when the serum ferritin level more than 1000 µg in order to prevent iron overload in transfusion dependent thalassemia. If these children is indicate for splenectomy, it plays an important role to reduce the blood transfusion requirement and any risk of infection, particularly the pneumococcal origin. However, this operation should not be performed until at least reached 5 years old of age. Bone marrow transplantation is potential curative way if there is compatible siblings donor.

For children who suffering thalassemia major who need for frequent blood transfusion, they may develop complications of chronic iron overload. These iron overload may effecting multiple organ damage such as hepatic, endocrine, pancreas, and cardiac organ. Liver has a

large capacity to produce proteins, which bind the iron and store it in the form of ferritin and haemosiderin, therefore, it can produce severe iron overload. Excess ferritin in hepar may develop to liver cirrhosis result from hemochromatosis or post-transfusion hepatitis. Liver cirrhosis also occur especially if with hepatitis B and hepatitis C infection.

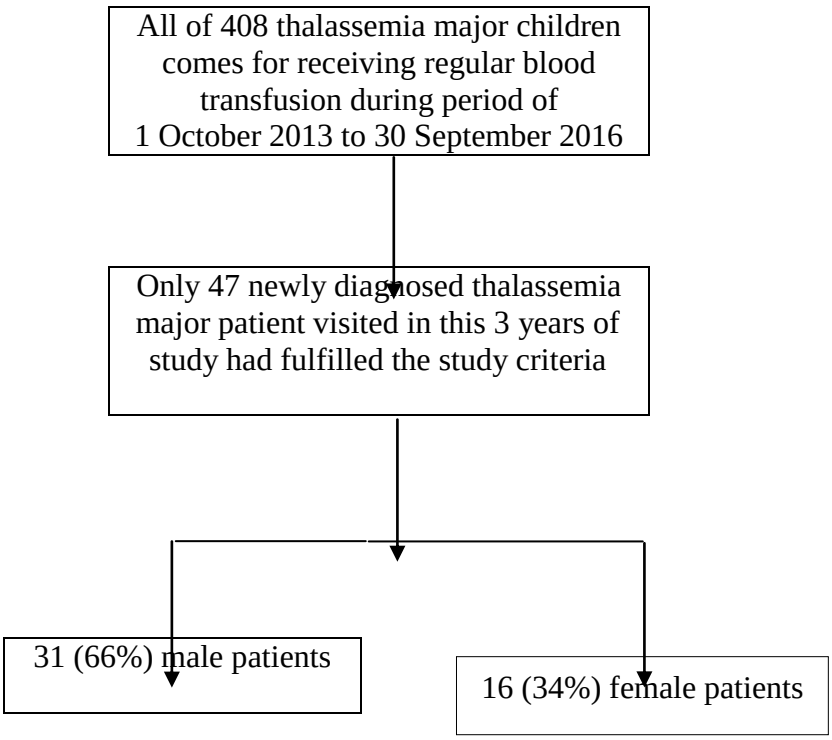
While the iron toxication in pituitary gland may cause delay in pubertal development and restrict the body growth. Meanwhile, the toxication of iron in pancreas lead to impaired glucose tolerance and diabetes mellitus. Moreover, there are some cardiac complication such as arrhythmias, pericarditis, and cardiac failure. Accumulation of excess iron result in hemochromatosis which deposited of iron in body tissues may cause bronze discolouration of skin and liver damage and usually die at their second or third decade of life because of cardiac failure.

METHODOLOGY

The study was done during September to November 2016. In this cross–sectional study, descriptive quantitative method were applied. The total sampling of 408 thalassemia major were registered for Outpatient Medical Record Installation Dr. Hasan Sadikin General Hospital Bandung from 1 October 2013 to 30 September 2016 (3 years) for undergo routine monthly transfusion. The inclusive criteria when there were only 47 subjects included in this study who are identified as a newly diagnosed thalassemia patients during a 3 years period of study. The patients also must have a completed data for one year of routine transfusion from the newly diagnosed of thalassemia.

After obtaining the approval from the Medical Ethics Committee and study permission from Education and Research Department of Dr. Hasan Sadikin General Hospital Bandung, the secondary data of medical record were collected by visiting Outpatient Medical Record Installation. The medical files which contain data information such as genders, age of first transfusion during diagnosis, transfusion interval, pre-haemoglobin level (haemoglobin value before receiving the transfusion), ferritin level, body weight for age, and spleen size and iron chelation therapy demand were reviewed. In some cases, we referred to the computerized registration number of the patient to complete information. When there have a data at diagnosis of thalassemia and one year later after the diagnosis, the study would be more better for comparing between both of these conditions via analytical study. However, since there have a limited time for doing this study, the descriptive study such an appropriated.

Achieves the objectives, the data collected were recorded on MS Excel spreadsheet program. All the variables were analysed from newly diagnosed of thalassemia major and after one year of transfusion by using SPSS for the descriptive statistics. Test of normality, Shapiro-Wilk and Kolmogorov-Smirnov were applied and $P<0.05$ was considered as significant. Values have been expressed as mean (SD), median (IQR,Min-Max), and percentages. SPSS's version is 11:5:1 and it is manufactured by IBM company.



Picture 1 : Protocol Subject Recruitment

RESULTS

The total 47 subjects of post diagnosis thalassemia major out from 408 patients who come for receiving regular transfusion at Dr. Hasan Sadikin General Hospital Bandung cases were studied. The clinical course was evaluated at diagnosis of thalassemia until received one year of blood transfusion. The characteristics of major thalassemia children was shown in table 1 provided.

Table 1. Characteristics of Thalassemia Major at Dr. Hasan Sadikin General Hospital Bandung (n=47)

Variables	Number
Ages, months (min-max)	12 (3-24)
Gender, male (%)	66
Age of first transfusion/diagnosis (months), median (IQR)	12 (2)

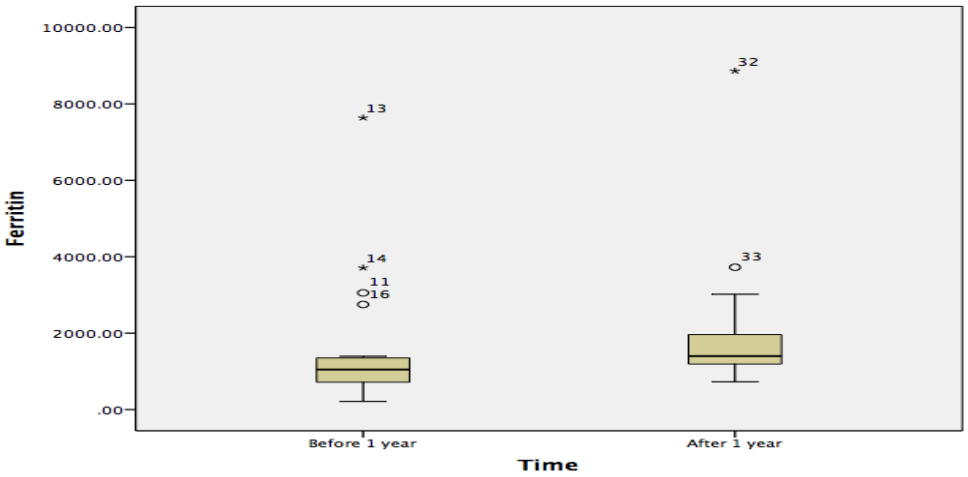
In table 1, the samples were not normally distributed for ages of children with a median age of 12 months ranging from 3 to 24 months. The distribution according to sex shows male predominance compared to female. The distribution data for age of first transfusion when diagnosis of thalassemia major also found to be not significant with a median age of 12 (±2) months.

Table 2. Clinical Manifestations Thalassemia Major at Dr. Hasan Sadikin General Hospital (n=47)

Variables	At diagnosis	One year transfusion
Transfusion intervals (weeks), mean (SD), median (IQR)	4 (1)	5 (1)
Hemoglobin level (g/dl), mean (SD)	8.0 (1)	7.5 (1)
Spleen size <3cm (%)	85.1	85.1
Weight–for–Ages <-2 SD of Z-score (%)	91.5	48.9
Iron chelation therapy, yes (%)	-	97

In table 2, the transfusion interval was significant with all patients were transfused monthly for every 4–5 weeks. At diagnosis, the patients were requiring packed red cell when their pre-haemoglobin level of 8.0±1 g/dl (mean+S.D). This level were slightly reduced to 7.5 ±1 g/dl (mean+S.D) after receiving 1 year transfusion. The spleen size had been reviewed and found to be constant in which 85.1% patients were having spleen size less than 3 cm at diagnosis and after 1 year later respectively.

Body weight for ages were highly improved when there is only 48.9% underweight patient were identified as compared to percentage at diagnosis with 91.5% were underweight. The patient were not given iron chelation therapy at diagnosis of thalassemia. However, almost 97% of the patient were received iron chelation therapy after receiving one year transfusion.



Picture 2. Boxplot Ferritin Level at Early Diagnosis and After One Year Transfusion of Thalassemia Major at Dr. Hasan Sadikin General Hospital (N= 19)

From 19 thalassemia major cases shown in picture 2, the mean serum ferritin level was increased up to 1132.43 (1037.56) ng/dl (mean+S.D) from 749.60 (820.82) ng/dl (mean+S.D) after the patient receiving multiple transfusion in one year. The ferritin level to assess iron overload surprisingly found to be increased which appropriate with 97% of the patients must required iron chelation therapy after receiving one year transfusion. The ferritin value result also tells us there are extreme value at 3054 ng/dl and 3019 ng/dl at diagnosis and after one year transfusion respectively.

DISCUSSION

Out of the 408 thalassemia major registered at Outpatient Medical Installation for regular transfusion, there are only 47 newly diagnosed thalassemia major patients who had fulfilled inclusive criteria in this study. This new diagnosis patients must have a completed secondary

data for one year of transfusion after diagnosis of thalassemia to be included in this study. Most of the new diagnosed thalassemia patient will be admitted to Dr. Hasan Sadikin General Hospital Bandung only for confirmatory diagnosis since this hospital as a top referral hospital in West Java Province and having a good accessibility and complete facilities in diagnosis the thalassemia. Most of the patients also tend to choose the nearest hospital or Community Health Care (*Rumah Sakit Umum Daerah*) from their living place for monthly regular blood transfusion. At this moment, the health service for thalassemia disease have provided in all Community Health Care (*Rumah Sakit Umum Daerah*) at West Java Province with undersupervised from Dr. Hasan Sadikin General Hospital Bandung.

In the present work, the ages of patients were not significant as the data not well distributed with a median age of 12 months ranging from 3 to 24 months. Besides, this situation is same to the study done by Sattari el al[8] in Iran, where their subjects for thalassemia major at the age ranges from 4 months to 65 years old with a median age of 14. The common things from both of this study where their ages of subjects were represented in median, minimum and maximum range terms as their data were not well distributed. However, this ages of patients are appropriate with the characteristics of beta thalassemia major in which the clinical presentations of thalassemia major usually occurs between the age of 6 and 24 months.[2]

The distribution data for age of first transfusion for diagnosis of thalassemia at Dr. Hasan Sadikin General Hospital at 12 months was not significant since data not well distributed. In reality, most of them were having their first transfusion at Community Health Care (*Rumah Sakit Umum Daerah*) or other general hospital in order to get initial treatment for anemic sign. Then, the patient will be referred to Dr. Hasan Sadikin General Hospital for a diagnosis of thalassemia major. Thus, the age of first transfusion for thalassemia major children would be more earlier than 12 months since they have a history of first transfusion at previous hospital. The first transfusion at this hospital will be given once the diagnosis for thalassemia major had been confirmed. A study done recently by Hira Tahir et al[10] from Pakistan reported 97.5% patients were receiving first transfusion once a definitive diagnosis of severe thalassemia is made.

The transfusion interval was significant with every 4–5 weeks interval for regular transfusion. Literature mentioned that the intervals varies from individual with the range of 2 to 6 weekly for the next transfusion.[11] A study done in the same service in India among 32 thalassemia cases were also reported that the transfusion interval typically every 15 to 25 days depending upon the severity of anemia.[12] It was a reality conditions for chronic transfuse patients to top up their blood back per monthly for upcoming survival.

The haemoglobin level not shown any relatively differences at diagnosis and after one year of transfusion with 8.0 g/dl and 7.5 g/dl respectively. The deciding for transfusion was done once the diagnosis for thalassemia major had been confirmed with laboratory haemoglobin < 7 g/dl on 2 occasions, or > 2 weeks apart.[2] However, if the haemoglobin >7 g/dl with any following criteria such as facial changes, poor growth or any clinical significant extramedullary haematopoiesis, a diagnosis of thalassemia can be made.[2] Since the patients having a history of transfusion at previous hospital before coming here for diagnosis, yet the haemoglobin level was not critically low when the diagnosis was made.

The reading after received one year of transfusion was 7.5 g/dl which still below the ultimate goals when the pre–haemoglobin level should be maintained between 9.0 and 10.5 g/dl or higher levels in every visited transfusion.[2,13] In Indonesia, this pre–haemoglobin level have

fulfilled the medical recommendation when the pre–haemoglobin level should be maintained ≤ 8 g/dl for receiving the next transfusion.[14]

In our study, there is 85% of the patients with spleen size were below than 3 cm at diagnosis and after received one year of transfusion respectively. It shows that most of the patients have a constant or remained same size of spleen from diagnosis of thalassemia until after receiving one year of transfusion. Previous research mentioned that splenectomy was commonly performed in nearly 60% of thalassemic children under 10 years of age in order to reduce frequency of blood transfusion and reduced iron overload.[15] It can be concluded that one year of transfusion were not obviously affected to the enlargement of spleen until allow them to undergo splenectomy.

The disturbance in growth development is one of the common complication in thalassemia major. In this study, it had been found that the percentages of underweight patient when weight for age was <–2 SD were reduced from 91.5% and dropped into 48.9% after one year of transfusion. Surprisingly, it shows a huge improvement in weight development when receiving one year of transfusion. This study result was appropriated with the literature when the patterns of growth are relatively normal until the age of 9-10 years when growth velocity begins to slow. In addition, thalassemia patient's growth was normal as to other non-thalassemia children until they reach puberty.

However, to be reminded the growth retardation would occurred when there is elevated level in serum ferritin during puberty.[16] This direct relationship between ferritin level and degree of growth retardation need to give attention as their growth getting developed. Accumulation of hemosiderin had been occurred causes deposited of iron in liver and spleen tissue. However, this hemosiderosis do not cause for any tissue damage after one year of transfusion. This matter can be proved when the result spleen size in this study were still remained constant.

Among 19 cases of thalassemia major, the patient revealed increasing a high ferritin level after one year of transfusion from mean 749±820 ng/dl to 1132±1037 ng/dl. Surprisingly, there is an extreme value at 3019 ng/dl of ferritin level after one year transfusion. It shows that one year of transfusion indicated the patients to receive iron chelation therapy as their ferritin level is more than 1000 ng/dl. It was synchronise with the result in this study where 97% patients need to received iron chelation therapy after one year of blood transfusion.

The reasons for increased in serum ferritin trends indicated the increase in iron burden of the body. Chronic transfusion would lead to iron overload (transfusional hemosiderosis) and excessive iron in the body is toxic to many tissues of liver, heart and endocrine organ.[2] In addition, serum ferritin is a good marker to monitor iron overload.[2] Thus, a prolonged monitoring serum ferritin level at regular intervals is very important to reduce the risk of vulnerable complications from iron overload in thalassemia major. Monitoring ferritin level with at least once in every 3 months was a practical method as management assessment.[12] The studies done by Chenta Jain et all[17] from India shown that the mean serum ferritin level was 2300±400 ng/dl then significantly reduced to 400±120 ng/dl after starting iron chelating agent.

In our study, deferiprone is the most common used by the patient in reducing the serum ferritin concentration. Previous study mentioned that deferiprone has been effective to decrease and stabilize the ferritin concentration as this medication need to administered everyday. In addition, it also helps to improve all the prognosis of patients.[18]

CONCLUSIONS

The findings of this study showed that all of the newly diagnosed thalassemia major at one year later were thalassemia dependent transfusion (TDT) major patients with ferritin level that keep up increasing.

Limitations in this study was this is a retrospective study by viewing the anamnesis, physical exam dan laboratory result from the medical files. Almost all the medical records do not have a computerized data. It may causes some error for the researcher to interpret and analyse the handwriting report from medical files. The suggestion for this research is the demographic data of patients should be completed properly. On medical record, all the handwritten report and medical results for each patient should be kept in one place and make it computerized in order easier for the doctor to review the history of illness.

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