MAK HILL Publications Research Journal of Medical Sciences

Research Article
doi: 10.59218/makrjms.2023.503.511

Thalassemia Major: Clinical Profile, Management, Complication and Outcome in Tertiary Care Center

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ABSTRACT

Thalassemia is an inherited disorder of autosomal recessive gene caused by impaired synthesis of one or more globin chains. The impairment alters production of normal hemoglobin (Hb). In people with beta thalassemia, low levels of hemoglobin lead to a lack of oxygen in many parts of the body. Affected individuals also have decreased red blood cells (anemia), which will manifest as pale skin, weakness, fatigue and serious complications. It is estimated that 1.5% of the world's population are carriers of β-thalassemia with an estimated 60,000 new carriers born each year. This is a prospective observational cohort study done in pediatric wards of two hospitals C. R. Gardi Hospital (C.R.G.H.) and associated hospitals, from September 2016 may 2018. Main aim of this study is: "Thalassemia major-'Clinical profile, management, complication and outcome in tertiary care center''. Out of 60 patients of thalassemia were enrolled and their demographic hematological profile was taken. The mean age was 10.2 years, 75% were males and 81% were Hindus, 40% belonged to upper lower class. Most common clinical features were (97%) icterus followed by (90%) pallor, 80% of thalassemia patients had moderate to severe hepatomegaly. Mean height was 105.77±14 cm, Mean Hb was 8.5±0.9 g dL^{-1}. Mean ferritin level was 1281.8±219.9 ng dL^{-1} , 45% of thalassemic patients had serum ferritin level between 1000-2000 ng dL^{-1} followed by 39% of patients had serum ferritin level more than 2500 ng dL^{-1}, Mean frequency of blood transfusion 16±2 times a year, 55% of had blood transfusion 5-10 times a year followed by 33% had frequency of blood transfusion 10-15 times a year and only 12% had frequency more than 15 times a year, Mean interval between transfusion 22±2 days, 73% had an interval of 15-25 days between two transfusion. About 86% had euglycemia and 10% had hyperglycemia when blood sugar was tested randomly. Tablet deferasirox was taken as chelating agent in all thalassemia patients, 51% of which were taking it after 2 years of age, 35% were had started between 1-2 years of age and only 13% started below 1 year of age. The common adverse reaction in thalassemic patients were diarrhea (26.1%), abdominal pain (23%), skin rash (20%), seizures (16%), blurring of vision (3%). Hepatitis C virus infection was found in 76% and hepatitis B surface antigen (HBsAg) was positive in 48% of thalassemia patients. Two patients (4%) out of 60 thalassemic patients had decreased left ventricular ejection fraction of 35-40%.

OPEN ACCESS

Key Words
Thalassemia, management, tertiary, clinical profile, complication

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Received: 1 July 2023
Accepted: 12 July 2023
Published: 15 July 2023

Citation: Mohit Sharma, Shreya Shrivastava, Sunil Kumar Kasundriya and Amit Kumar Singh, 2023. Thalassemia Major: Clinical Profile, Management, Complication and Outcome in Tertiary Care Center . Res. J. Med. Sci., 17: 503-511, doi: 10.59218/makrjms.2023.503.511

INTRODUCTION

Thalassemia is an inherited disorder of autosomal recessive gene caused by impaired synthesis of one or more globin chains. The impairment alters production of normal hemoglobin (Hb).

Thalassemia causes varying degrees of anemia, which can range from significant to life threatening. People of Mediterranean, Middle Eastern, African and Southeast Asian descent are at higher risk of carrying the genes for thalassemia.

Thalassemia is caused by mutations that decrease hemoglobin synthesis and red cell survival. Thalassemia is caused by decreased or absent production of one type of globin chain, either alpha or beta globin chain. These hematologic disorders range from asymptomatic to severe anemia that can cause significant morbidity and mortality.

It was first recognized clinically in 1925 by Dr. causas Cooley, who described a syndrome of anemia with microcytic erythrocytes. Then it was called Cooley's anemia. Later Wipple and Bradford renamed this disease as "Thalassemia". Because it was found in the region of the Mediterranean Sea (thalasa is an old Greek word for sea)[1].

Beta-thalassemia includes three main forms: Thalassemia major variably referred to as "Cooley's Anemia" and "Mediterranean Anemia", Thalassemia intermedia and Thalassemia minor also called "beta-thalassemia carrier", "beta-thalassemia trait" or "heterozygous beta-thalassemia".

Beta thalassemia is a disorder that reduces the production of hemoglobin. Hemoglobin is the iron-containing protein in red blood cells that carries oxygen to cells throughout the body.

In people with beta thalassemia, low levels of hemoglobin lead to a lack of oxygen in many parts of the body. Affected individuals also have decreased red blood cells (anemia), which will manifest as pale skin, weakness, fatigue and serious complications.

It is estimated that 1.5% of the world's population are carriers of β- thalassemia with an estimated 60,000 new carriers born each year. Southeast Asia accounts for about 50% of the world's carriers while Europe and the Americas jointly account for 10-13% of the world carriers.

Beta thalassemia is widespread throughout the Mediterranean with uneven distribution in Greece and Italy but less common at the western end of the Mediterranean and appears to be little in France except in those of Italian or Spanish descent. The disorder is however common in the Middle East and west Asia and it is probably the commonest inherited haemoglobine disorder in India. Beta-thalassemia is reported to be between 3-7% in most of North Africa. India is a large Southeast Asian country with a population of over one Billion. An estimated 1-3% of the population are carriers of beta thalassemia, a figure rising up to 17% in some ethnic groups[2].

In India, prevalence of Thalassemia is very high in Punjabis, Sindhs, Gujaratis, Bengalis, Parsee, Lohana and certain tribal communities and in Northern, Western and Eastern part, while it is much less in the south of India.

About 6,000 children are born with thalassemia major each year, more than 30% of birth with a major thalassemia syndrome in South East Asia.

Beta thalassemia is classified into two types depending on the severity of symptoms: Thalassemia major (also known as Cooley's anemia) and thalassemia intermedia. Of the two types, thalassemia major is more severe.

The signs and symptoms of thalassemia major appear within the first 2 years of life. Children born with thalassemia are normal at birth but major symptoms in early childhood are anemia and mild jaundice. There is always some degree of hepatosplenomegaly, bone changes are variable and range from none to severe deformity, identical to that seen in β-homozygous thalassemia. Costin explained that the child who is not transfused fails to thrive and shows growth retardation early in life, in association with severe anemia and hypersplenism, he also observed the poor musculature, reduction of body fat, poor appetite and lethargy in thalassemic children. Thalassemia symptoms include fatigue, weakness of the body and shortness of breath. The affected person will have a pale appearance of his skin and he would seem to be more irritable than normal. The skin may also take a yellow discoloration and the abdomen may seem to be protruding. Other thalassemia symptoms are slow growth, dark colored urine and facial bone deformities, shortness of breath, yellow skin coloring. Such thalassemia symptoms or signs may occur at birth or might take about two years of life, to have their occurrence.

Overtime, an influx of iron-containing hemoglobin from chronic blood transfusions can lead to a buildup of iron in the body, resulting in liver, heart and hormone problems. The aims and objective of this study is to study the clinical features, complications in Beta-thalassemia patient and outcome from Ujjain district and so that timely intervention can be done to prevent complications.

Aims and objectives: This is a prospective observational cohort study done in pediatric wards of two hospitals C. R. Gardi Hospital (C.R.G.H.) and associated hospitals, from September 2016 may 2018. Main aim of this study is- 'Thalassemia major- 'Clinical profile, management, complication and outcome in tertiary care center''.

MATERIALS AND METHODS

Study design: Observational and prospective study.

Study duration: September 2016 may 2018.

Study setting: The study was conducted in pediatric wards of two hospitals C. R. Gardi Hospital (C.R.G.H.) and associated hospitals.

Study participants
Inclusion criteria:

- Children with diagnosis of thalassemia
- Age group 6 months and above
- Thalassemia children who are on regular blood transfusion with or without iron chelation therapy

Exclusion criteria: Children with other causes of anemia like nutritional anemia, aplastic anemia, sickle cell anemia.

Sample size: To calculate sample size it was assumed that 50% of patients of Thalassemia will have at least one known complications thus to detect at least 50% of complication with a difference of +/-20% around the assumed complications rate of 50% with a power of 80 two sided alpha 0.05 estimated minimum sample size is 103.

Data collection: Children who fulfill the inclusion criteria for the study will be selected. After proper clinical examination and preliminary investigation, the child will be subjected to clinical outcome and complication. The data will collect on proper proforma.

The data thus collected will be subjected to statistical analysis.

Pre and post transfusion hemoglobin and serum ferritin level, complete hemogram, Hb electrophoresis, peripheral blood smear, urine urobilinogen are done as a part of standard care for thalassemia patients.

Serum ferritin level will be estimated by chemiluminescent immunometric assay[3].

Haemoglobin estimation will be done by Beckmen Coulter machine using cyanmethemoglobin automated method.

Statistical analysis: The data was entered in Epidata Entry (version 3.1) and then transferred to Stata 10.0 (Stata Corp. College Station, Texas, USA) software for statistical analysis. Frequency and percentages are presented for categorical data. Chi square test was used for measuring association between different categories. Binary logistic regression were applied and calculate odd ratio. A p-value less than or equal to 0.05 was considered significant. t-test was used for comparing the mean duration of stay.

OBSERVATION AND RESULTS

Table 1 shows that 50% of thalassemic patients belonged to 5-10 years of age, 28% of patients belonged to 6 months -5 years and 22% belonged to >10 years of age.

Table 2 shows that 75% of thalassemic patients were males.

Table 3 shows 81% of thalassemic patients belonged to Hindu religion and 19% belonged to population.

Table 4 shows that 40% of thalassemic patients belonged to upper lower class, 38% patients belonged to lower class, 12% of patients belonged to lower middle class and only 10% patients belonged to upper middle class.

Table 5 shows various clinical features with which patients presented icterus (97%), pallor (90%), facial changes (79%), loss-of-appetite (60%), lethargy (60%), skin-pigmentation (58%), breathlessness (33%), skeletal changes (30%), diarrhea (27%), fever (14%), oliguria (12%) respiratory distress (17%), hematemesis (16%), dark colored urine (11%), vomiting (7%), edema (2%).

Table 6 shows that 50% of thalassemia patients were presented with severe hepatosplenomegaly followed by 30% patients with moderate hepatosplenomegaly and only 20% patients with mild hepatosplenomegaly.

Table 7 shows that 46% of thalassemic patients presented between -1 SD and -2 SD followed by 20% thalassemic patients presented between -3 SD and -2SD followed by 20% thalassemic patients between less than <-3SD and only 14% thalassemic patients between -1 SD and Median. Mean height was 105.77 cm (SD±13.79).

Table 8 that 67% of thalassemic patient presented with severe anemia and 33% of thalassemic patients with moderate anemia. Mean hemoglobin level: 8.2±2 g dL^{-1}.

Table 1: distribution of thalassemia patients according to age

Age	N = 60
6 month 5 Years	17 (28%)
5-10 years	30 (50%)
>10 years	13 (22%)

Table 2: Distribution of thalassemia patients according to gender

Gender	n = 60
Male	45 (75%)
Female	15 (25%)
Total	60

Table 3: Distribution of thalassemia patients according to religion

Religion	N = 60
Hindu	49 (81%)
Muslim	11 (19%)
Total	60

Table 4: Distribution of thalassemia patients according to socioeconomic status (modified kuppuswamy scale)

Socioeconomic status	N = 60
Upper middle	6 (10%)
Lower middle	7 (12%)
Lower	23 (38%)
Upper lower	24 (40%)
Total	60

Table 5: Distribution of thalassemia patients according to clinical features

Clinical features	N = 60
Lcterus	58 (97%)
Pallor	54 (90%)
Facial changes	47 (79%)
Loss of apeptite	36 (60%)
Lethargy	36 (60%)
Skin pigmentation	35 (58%)
Fatigue	22 (37%)
Breathlessness	20 (33%)
Skeletal changes	18 (30%)
Diarrhea	16 (27%)
Fever	14 (23%)
Oliguria	12 (20%)
Respiratory distress	10 (17%)
Hematemesis	10 (16%)
Dark colored urine	7 (11%)
Vomiting	4 (7%)
Edema	1 (2%)

Table 6: Distribution of thalassemia patients according to hepato-splenomegaly

Hepatospleenomegaly	N = 60
Severe	30 (50%)
Moderate	18 (30%)
Mild	12 (20%)
Total	60

Table 7: Distribution of thalassemia patients according to height

Anthropometry	N = 60
Between -1 SD and -2 SD	28 (46%)
B/W -3 SD and -2 SD	12 (20%)
<-3 SD	12 (20%)
B/W -1 SD and median	8 (14%)
Total	60

Table 8: Distribution of thalassemia patients according to hemoglobin levels

Age	Modreate	Severe
<1 year	1 (1.6%)	2 (3.3%)
2-3 years	6 (10%)	7 (11.6%)
4-6 years	2 (3.3%)	12 (20%)
7-9 years	4 (6.6%)	3 (5%)
>9 years	7 (11.6%)	16 (27%)
Total	20 (33%)	40 (67%)

Table 9: Distribution of thalassemia patients according to frequency of blood transfusion in a year

Frequency of blood transfusion (times year^{-1})	N = 60
5-10 times year^{-1}	33 (55%)
10-15 times year^{-1}	20 (33%)
>15 times year^{-1}	7 (12%)
Total	60

Table 9 shows that 55% of thalassemia patients had frequency of blood transfusion 5-10 times per year followed by 33% of patients between 10-15 times per year and only 12% patients more than 15 times per year. Mean frequency of blood transfusion 16±2 times a year

In this study 73% of thalassemia patients were transfused blood between 15-25 days followed by 16% of patients were transfused between 25-35 days and only 11% of patients were transfused blood between 35-45 days. Mean interval between transfusion 22±2 days (Table 10).

Table 11 and shows that 10% 0f thalassemic patients were presented with hyperglycemia, 4% of thlassemic patients with hypoglycemia and 86% of patients were euglycemia.

Table 12 shows that 51% of thalassemia patients started deferasirox more than 2 years of age, 35% of patients started deferasirox between 1-2 year while 13% of patients started deferasirox less than 1 year of age.

Table 10: Distribution of thalassemia patients according to interval between transfusion (days)

Interval between transfusions (days)	N = 60
15-25 days	44 (73%)
25-35 days	10 (16%)
35-45 days	6 (11%)
Total	60

Table 11: Distribution of thalassemia patients according to random blood sugar levels

Blood sugar	N = 60
Euglycemia	52 (86%)
Hyperglycemia	6 (10%)
Hypoglycemia	2 (4%)
Total	60

Table 12: Distribution of thalassemia patients according to age of onset of drug chelating agent (deferasirox)

Age of onset	N = 60
<1 year	8 (13%)
1-2 year	21 (35%)
>2 year	31 (51%)
Total	60

Table 13: Distribution of thalassemia patients according to adverse drug reaction

Adverse drug reaction	N = 60
Diarrhea	16 (26%)
Abdominal pain	14 (23%)
Skin rash	12 (20%)
Seizure	10 (16%)
Blurring of vision	2 (3%)
Total	60

Table 14: Distribution of thalassemia patients according to hepatitis c virus infection

Blood transmitted infection (HCV)	N = 60
Positive	46 (76%)
Negative	14 (24%)
Total	60

Table 15: Distribution of thalassemia patients according to hbsag infection

Blood transmitted infection (hepatitis b)	N = 60
Negative	31 (52%)
Positive	29 (48%)
Total	60

Table 15: Distribution of thalassemia patients according to echocardiographic changes

Echo changes	N = 60
Normal (LVEF >55-60%)	58 (96%)
Abnormal (LVEF <55%)	2 (4%)
Total	60

Table 13 shows that most common adverse drug reaction found was Diarrhea (26%), followed by abdominal pain (23%) followed by Skin rash (20%) followed by seizure(16%) and in only 3% of patients blurring of vision was found.

Table 14 shows that 76% of thalassemia patients had hepatitis c virus infection.

Table 15 shows that 52% of thalassemic patients had hepatitis b virus infection

Table 16 shows that 4% of thalassemia patients were had decreased left ventricular ejection fraction (LVEF)

DISCUSSIONS

In present study out of 60 children 75% (n = 45) were males and 25% (n = 22) were females. It is comparable to the study done by Karimi in Iran done

on 50 Thalassemia major children out of which 66% were (n = 33) were males and 34% (n = 17) were females. A similar study done by Azankeivan included 104 thalassemia major patients out of which 63% (n = 75) were male and 37% (n = 39) were female.

The prevalence of β-thalassemia trait varies between 3-17% because of consanguinity and caste and area endogamy[1]. Every year, ten thousand children with β-thalassemia major are born in India, which constitutes 10% of the total number in the world.5 HbE thalassemia is common in north-east parts of India.

In Present study group comprised of patients ranging between 6 month to 18 years with a mean age of 10.20+/-3 years. Similar observation Arora study at Lady Harding Medical College, New Delhi, studied 30 children and 20 matched controls. The mean age of study group 11.83+/-1.91 years (range 9-17 years) and that of control group 12+/-2.17 years (range 9-17 years) was comparable. Arie Bacalo in an Arab hospital studied 17 children aged 6-17 years (average 11.2 years).

Mean heamoglobin in present study was 6.244 (+/-1.66) g dL^{-1} which is much lower than most of studies done. In study by Arora found mean heamoglobin of patient was (9.87+/-1.45 g dL^{-1}). A similar study done by Kanj mean hemoglobin was (8.8+/-1.1) g dL^{-1}. In a study done by Carnelli D'Angelo, Pecchiari mean hemoglobin was (9.3+/-1) g dL^{-1} this reason behind such a low mean value of hemoglobin was because parents stay away from hospital, ignorance and literacy .

In present study 81% of thalassemic patients belonged to Hindu religion and 19% belonged to Muslims. A Similar study done by Padma Bhatia at Department of Community Medicine, Gandhi Medical College, Bhopal, Madhya Pradesh found that Religion-wise distribution showed maximum cases 134 (74.4%) were Hindus followed by 37 (20.5%) Muslims and 9 (5.0%) others.

In present study 40% of thalassemic patients belonged to upper lower class, 38% patients belonged to lower class,12% of patients belonged to lower middle class and only 10% patients belonged to upper middle class. Similar study done by Navjot at Christian medical college Ludhiana found that 51.4% of thalassemic children had poor quality of life, whereas 48.6% of children in control group had high quality of life. There was no statistically significant association between quality of life and socioeconomic status in both groups.

In present study various clinical features with which patients presented were icterus (97%), pallor (90%), facial changes (79%), loss-of-appetite (60%), lethargy (60%), skin pigmentation (58%), breathlessness (33%), skeletal changes (30%), diarrhea (27%), fever (14%), oliguria (12%) respiratory distress (17%), hematemesis (16%), dark colored urine (11%),vomiting (7%), edema (2%). Similar study done by Kaustubh Chattopadhyay at N.R.S. Medical College, Kolkata found that hepatomegaly was the most common presenting complaint among the study population (66.3%), followed by jaundice (53.9%), splenomegaly (47.5%) , thalassemic facies (53.2%) and Growth retardation (23.6%).Skin pigmentation (16.5%), Ascites (3%) and edema (3%).

In response to anemia, body secretes more of erythropoietin (EPO). Patients with high HbF levels of EPO results in increase in erythropoiesis by 10-30 folds resulting in increase in metabolic activity, nutritional depletion of folic acid, growth stunting, increased cardiac load, congestive cardiac failure, etc. Splenomegaly primary occurs secondary to increased entrapment of blood and to some extent due to extramedullary hematopoiesis. Large spleen may become hyperactive thus leading to exacerbation of anemia, increased blood requirements, thrombocytopenia and leucopenia. Such a state is termed as hypersplenism.

In present study 46% of thalassemic patients had height between -1 SD and -2 SD followed by 20% thalassemic patients had height between -3 SD and -2 SD followed by 20% thalassemic patients had there height less than <-3 SD Only 14% thalassemic patients had there height -1 SD and median. Similar study done by Muhammad Shahid Aslam et al in military hospital Rawalpindi Pakistan found that out of 100 patients of β-thalassemia major 57.0% (n = 57) of patients were found to be short statured while 43.0% (n = 43) were with normal height.

The pathogenesis of growth failure in thalassemia is multifactorial and is mainly due to transfusional iron overload and resulting endocrinopathies (GH deficiency, hypothyroidism, diabetes), nutritional deficiencies and intensive use of chelating agents particularly deferrioxamine. Other etiologies particularly in sub optimally treated children are increased metabolism, chronic anemia and hypoxia. The anterior pituitary is particularly sensitive to iron associated free radical oxidative stress. Even a modest amount of iron deposition in anterior pituitary by MRI can interfere with its function. Dysregulation of the GH insulin like growth factors axis leads to growth hormone deficiency and growth deceleration. Balgir Hematology blood transfusion)[4].

All children with Beta thalassemia major >10 years should undergo standing and sitting height every 6 months, bone age, growth hormone stimulation, insulin like growth factor (IGF)-1 level and IGF-BP3 level.

Frequent blood transfusion should be considered in patients with growth failure with reassessment for

tapering or withdrawal when a sustained clinical benefit is achieved. Thalassemia a global health problem[5,6].

In present study 50% of thalassemia patients presented with severe hepatosplenomegaly followed by 30% patients with moderate hepatosplenomegaly and only 20% patients with mild hepatosplenomegaly. Similar study done by Santosh Kumar at Department of Pediatrics, MGM Medical College and LSK Hospital, Kishanganj, Bihar found Out of 211 patients hepatomegaly was the most common clinical finding among the study population (57.8%), followed by splenomegaly (54.9%).

In present study 67% of thalassemic patient presented with severe anemia and 33% of thalassemic patients with moderate anemia.

In present study 55% of thalassemia patients had frequency of blood transfusion 5-10 times per year followed by 33 % of patients between 10-15 times per year and only 12% patients more than 15 times per year. Similar study done by Neeraj shah at NHL Municipal Medical College, Ahmedabad found that 36% of thalassemic patients had blood transfusion more than 15times per year, 34% of thalassemic patients had blood transfusion between 5-10 times per year and only 28% of thalassemic patients had transfused blood more than 10 times per year.

In present study 73% of thalassemia patients were transfused blood between 15-25 days followed by 16% of patients were transfused between 25-35 days and only 11% of patients were transfused blood between 35-45 days. A Similar study done by Neeraj shah at NHL Municipal Medical College, Ahmedabad found that 42% of thalassemic patients were transfused blood between 15-25 days followed by 38% of thalassemic patients had transfused blood between 25-35 days and only 20 % of thalassemic patients transfused blood between 25-35 days.

Severe anemia with hemoglobin <7 g% for more than 2 weeks is widely accepted as an indication to start blood transfusion. The goal should be aimed to maintain a pre-transfusional Hb level of 9-10 g dL^{-1} and a post-transfusion Hb level of 13-14 g dL^{-1}. Such regime generally prevents growth impairment, organ damage and bone deformities. Care should be taken to avoid faster transfusion exceeding 5 mL kg^{-1} hrs^{-1} and amount of transfused RBC should not exceed 15-20 mL kg^{-1} day^{-1}. The frequency of transfusion is usually every 2-4 weeks (Ramesh agarawal an overview of Thalassemia)[7].

In present study 49% of thalassemic patients had ferritin levels between 1000-2500 ng mL^{-1} followed by 39% of thalassemic patients more than 2500 level ng mL^{-1} and only 12% of thalassemic patients had ferritin level less than 1000 ng mL^{-1}. Similar study done by Saraya, Department of Pediatrics and Computer Center, AIIMS Delhi studied Serum ferritin levels in 64 patients with beta homozygous thalassemia (BHT), 120 patients with beta heterozygous thalassemia and 46 normal subjects. Incidence of iron overload seen in 32 Beta heterozygous thalassemia cases was similar in untransfused and transfused cases. Among heterozygotes thalassemia patients, iron stores were depleted in 24 (20%) patients, mostly females 70.8% and 29.2% of males.

The iron burden on the body can be estimated by means of serum ferritin, iron and TIBC levels. The estimation of serum ferritin levels is the most commonly employed test to evaluate iron overload in β-thalassemia major. The association between serum ferritin and levels of body iron are well-established and the test is easy to perform compared with other tests for iron overload. (Panchal and Patel Iron chelation status in young children with Thalassemia)[8].

In present study 51% of thalassemia patients started chelating agent by Deferasirox more than 2 years of age, 35% of patients started deferasirox between 1-2 year while 13% of patients started Deferasirox at less than 1 year of age. Similar study done by Dhaval Thako conducted a study on Efficacy and Safety of Deferasirox in Pediatric Patients of Thalassemia at a Tertiary Care Teaching Hospital B.J. Medical college and Civil hospital Ahmedabad found that 64% of thalassemic patients started deferasirox more than 2 years of age, 26 % of thalassemic patients started deferasirox between 1-2 years of age and only 10% started deferasirox less than 1 year of age.

Iron overload in these children develops secondary to two main factors:

- Increased iron absorption from gut secondary to excessive erythropoiesis
- Trasnsfusional iron which plays an important role. Normally iron is bound to plasma (transferrin) and storage proteins and there is hardly any level in form of toxic free radicals

In thalassemic patients transferring and other iron binding proteins get saturated and free iron radicals cause wide spread tissue damage trough production of hydrogen peroxide (H_2O_2) and hydroxyl ions affecting liver, heart and endocrine organs. Iron in the liver gets deposited in parenchyma and retico-endothelial cells of liver leading to development of progressive liver fibrosisc, cirrhosis and eventually carcinoma of liver.

Iron overload in the heart cause extensive myocardial fibre disruption and variable fibrosis which increases the uptake of toxic non transferrin bound iron (NTBI) cause further cardiac damage .Free hydroxyl radicals causes damage to the lysosomal, membrane of myocytes further affecting cardiac

functions adversely. Iron deposition in conducting system may lead to fatal arrhythmias. (Piyush gupta, PG Text book of pediatrics volume-2)

The introduction of the iron chelator deferoxamine greatly ameliorates the effects of iron toxicity but long-term cardiac mortality has been very disappointing[9,10]. There is strong evidence that long-term deferoxamine chelation does not effectively prevent myocardial siderosis in a majority of patients. Deferiprone, the first approved oral chelator, has been shown in randomized controlled trials to be effective monotherapy at 100 mg kg^{-1} day^{-1} in treating mild to moderately severe myocardial iron loading (myocardial T2×8-20 ms), significantly improving both myocardial iron and ejection fraction[11] and the combination of deferiprone at 75 mg kg^{-1} day^{-1} with deferoxamine is likewise effective[2]. However greater total iron clearance is seen with combined treatment[12-13], which suggests that it might be useful for severe myocardial siderosis (T2×< 10 ms).

The conventional treatment at many centers for severe myocardial siderosis with heart failure is long-term, continuous, high-dose intravenous deferoxamine. Several small studies have confirmed that this approach is effective and reversal of cardiomyopathy is possible.

Combined chelation therapy in this situation might be effective, yet prospective trials examining the treatment of severe cardiac siderosis are lacking.

The inevitable consequence of regular life-saving transfusions in thalassemia major is the accumulation of excess iron within tissues. This causes progressive organ damage and dysfunction which, without treatment, can lead to an increase in morbidity and mortality[13]. For patients requiring regular blood transfusions, iron chelation may represent life-saving therapy. A landmark study investigating role of desferoxamine (Desferal®) in prevention of complications of transfusional iron overload showed that survival to at least 25 years of age in poorly chelated β-thalassemia major patients was just one-third that of patients whose iron levels were well managed by deferoxamine[11]. The optimal age for initiating iron chelation therapy in patients with severe thalassemia remains uncertain, although in theory it should begin as early as possible to prevent growth and developmental defects. Guidelines from the Thalassemia International Federation recommended that chelation therapy is initiated when serum ferritin levels reach approximately 1000 ng mL^{-1}, which usually occurs after the first 10-20 transfusions or around 2-3 years of age.

Since the body has no effective means of effectively removing iron, the only way to remove excess iron is to use iron chelators. The major step forward in improving survival and reducing complications was the introduction, of the chelating agent deferoxamine, used as a subcutaneous infusion. Two oral chelators, deferiprone and deferasirox, have recently become available, making therapy easier and more efficacious. Compliance, although improved by the switch to oral therapy, still presents a problem and is the major obstacle to effective prevention of iron overload. The orally active chelators seem to be more effective in gaining access to the chelatable iron pool of cardiomyocytes, binding labile iron and attenuating reactive oxygen species formation. Other study showed that the combination therapy is associated with lower risk of mortality.

In present study various adverse drug reactions found were Diarrhea (26%), followed by abdominal pain (23%) followed by Skin rash (20%) followed by seizure (16%) and in only 3% of patients blurring of vision was found. Similar study done by Dhaval Thako conducted a study on Efficacy and Safety of Deferasirox in Pediatric Patients of Thalassemia at a Tertiary Care Teaching Hospital B.J. Medical college and Civil hospital found that a total of 117 ADRs were observed in 52 patients from 19498 doses, most common being diarrhea (46%), raised serum creatinine (28%), raised hepatic enzymes (26%), abdominal pain (26%) and skin rashes (24%).

Diarrhea was most common drug adverse reaction in present study. Diarrhea in these patients can be because of a faulty drug administration technique causing improper drug dispersion. Emphasis should therefore be laid on educating the patient/caretakers at each visit to ensure better drug compliance and to reduce the incidence of adverse reactions such as diarrhea.

In present study, n = 46 (76%) of thalassemia patients had hepatitis C virus infection and n = 29 (48%)of thalassemic patients had Hepatitis B virus infection . Similar study done by Kheya Mukherjee at Nilratan Sircar Medical College, Kolkata, West Bengal found that out of 207 patients of beta-thalassemia, who had received at least 10 transfusions were tested .The overall number of anti-hepatitis C antibody seropositivity was 51 (24.6%) and that for hepatitis B surface antigen positivity was 7 (3.38%). The prevalence rate for hepatitis B surface antigen was in agreement with average national values but in case of anti-HCV antibodies the prevalence rate values were comparatively much higher.

Hepatitis C virus is a hepatotrophic, single strand ribonucleic acid (RNA) virus of family Flaviviridae and genus hepacivirus. An estimated 180 million people worldwide are chronically infected with hepatitis C with the global prevalence being around 2% and 3-4 million persons getting newly infected each year. A large number of genotypes and subtypes have been identified among hepatitis C virus isolates from all over

the world.7 Of the six main groups of sequence variants, corresponding to types 1-6, genotype 3 is the most prevalent genotype in patients with chronic hepatitis C in North and Central India and is associated with significant hepatic steatosis and fibrosis.

Several studies on voluntary or mixed donors have noted a prevalence of hepatitis C below 2% in India and 0.71% in West Bengal. It should be remembered that HCV hepatitis is more threatening than HBV hepatitis due to a greater risk of chronic liver disease.10 It is estimated that about 2 billion people have serological evidence of current or past HBV infection worldwide, of which more than 350 million have chronic HBV and 1.2 million die annually from chronic hepatitis, cirrhosis and hepatocellular carcinoma[11]. The global prevalence of HBV infection varies widely and its endemicity ranges from high (≥8%) to intermediate (2-7%) and low (<2%). 12,13 In India, HBsAg prevalence among general population ranges from 2-8%, placing India in intermediate HBV endemicity zone and the number of HBV carriers is estimated to be 50 million. Compared to other parts of India, the distribution patterns of HBV genotypes/sub-genotypes and mutants is characteristically distinct in eastern part, where in addition to HBV genotypes A and D, genotype C is also present in a comparable proportion.14

Fortunately, HBV infection can be, to a great extent, prevented by a pre-transfusion immunization, HCV infection has gained importance particularly as one of the major complications in multiple-transfused patients during the last decade. This is especially true for countries where HCV is more prevalent in general population and therefore also amongst blood donors. The prevalence rate of seropositivity increases with the number of transfusions[13]. However, since no vaccine is so far available against hepatitis C, the only effective protective measure against this virus is provision of HCV negative blood for transfusion in thalassemia patients.

In present study, 4% of thalassemic patients on echocardiography had decreased left ventricular ejection fraction (LVEF) and 86% patients of thalassemia had normal ejection fraction (≥60%). Similar study done by Sambhaji and Chate at Department of Pediatrics, LTMMC and GH, Sion, Mumbai, Maharashtra found that out of 32 thalassemic patients left Ventricular Ejection Fraction (LVEF) on 2-D echocardiography was ≥60% in all the 32 patients.

Cardiac structure and function in thalassemia are mainly affected by two competing factors: Iron overload and increased cardiac-output (CO). The cardiac iron deposition results in a decrease of left ventricular function. Despite the advances in therapeutic management of thalassemia major and the resulting substantial improvement of patient's survival, heart disease always represented and still remains the primary cause of mortality and a major cause of morbidity[14]. All the 32 patients had normal left ventricular ejection fraction. (LVEF ≥60%) as assessed by 2-Dechocadiography. A diastolic dysfunction on Doppler echocardiography was present in 19 (59.37%) patients and absent in remaining 13 (40.63%) patients. Out of 19 patients having diastolic dysfunction, cardiomegaly on chest radiograph was present in 17 patients. (p = 0.02) Observations similar to our study were made by Addison *et al*.[2] studied 32 patients with thalassemia major and found impaired diastolic Doppler indices in patients having normal systolic function.14Hankins et al studied 47 patients with transfusion dependent anemias. While most patients had normal LV systolic function, 42% patients had signs of diastolic dysfunction, suggesting diastolic dysfunction to be an early sign of myocardial dysfunction in cardia chemo siderosis. Hou their study of 45 thalassemic children similarly showed that Left ventricular diastolic filling variables by echocardiography are important predictors of the outcome of patients with transfusion dependent beta-thalassemia major.

CONCLUSION

Out of 60 patients of thalassemia were enrolled and their demographic hematological profile was taken. The mean age was 10.2 years, 75% were males and 81% were Hindus, 40% belonged to upper lower class.

Most common clinical features were (97%) icterus followed by (90%) pallor, 80% of thalassemia patients had moderate to severe hepatomegaly. Mean height was 105.77±14 cm , Mean Hb was 8.5±0.9 g dL^{-1}.

Mean ferritin level was 1281.8±219.9 ng dL^{-1}, 45% of thalassemic patients had serum ferritin level between 1000-2000 ng dL^{-1} followed by 39% of patients had serum ferritin level more than 2500 ng dL^{-1}, Mean frequency of blood transfusion 16±2 times a year , 55% of had blood transfusion 5-10 times a year followed by 33% had frequency of blood transfusion 10-15 times a year and only 12% had frequency more than 15 times a year, Mean interval between transfusion 22±2 days, 73% had an interval of 15-25 days between two transfusion., 86% had euglycemia and 10% had hyperglycemia when blood sugar was tested randomly.

Tablet deferasirox was taken as chelating agent in all thalassemia patients, 51% of which were taking it after 2 years of age, 35% were had started between 1-2 years of age and only 13% started below 1 year of age.

The common adverse reaction in thalassemic patients were diarrhea (26.1%), abdominal pain (23%),

skin rash (20%), seizures (16%), blurring of vision (3%). Hepatitis C virus infection was found in 76% and hepatitis B surface antigen (HBsAg) was positive in 48% of thalassemia patients.

Two patients (4%) out of 60 thalassemic patients had decreased left ventricular ejection fraction of 35-40%.

REFERENCES

1. Cooley, T.B., 1946. American Journal of Diseases of Children, Chicago. Am. J. Dis. Child., 37: 29-30.
2. Addison, G.M., M.R. Beamish, C.N. Hales, M. Hodgkins, A. Jacobs and P. Llewellin, 1972. An immunoradiometric assay for ferritin in the serum of normal subjects and patients with iron deficiency and iron overload. J. Clin. Pathol., 25: 326-329.
3. Letsky, E.A., F. Miller, M. Worwood and D.M. Flynn, 1974. Serum ferritin in children with thalassaemia regularly transfused. J. Clin. Pathol., 27: 652-655.
4. Weatherall, D.J., 1987. Common genetic disorders of the red cell and the 'malaria hypothesis'. Ann. Trop. Med. Parasitol., 81: 539-548.
5. Weatherall, D.J. and J.B. Clegg, 1996. Thalassemia: A global public health problem. Nat. Med., 2: 847-849.
6. Allen, S.J., A. O'Donnell, N.D.E. Alexander, M.P. Alpers, T.E.A. Peto, J.B. Clegg and D.J. Weatherall, 1997. α^{+}-thalassemia protects children against disease caused by other infections as well as malaria. Proc. Nat. Acad. Sci., 94: 14736-14741.
7. Bank, A. and P.A. Marks, 1966. Excess α chain synthesis relative to β chain synthesis in thalassaemia major and minor. Nature, 212: 1198-1200.
8. Borgna-Pignatti, C., S. Rugolotto, P.D. Stefano, H. Zhao, M.D. Cappellini*et al*., 2004. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. Haematologic, 89: 1187-1193.
9. Bradford, W.L. and J. Dye, 1936. Observations on the morphology of the crythmytes in Mediterranean disease thalassemia (erythroblastic anemia of cooley). J. Pediatr., 9: 12-13.
10. Duke, M. and W.H. Abelmann, 1969. The hemodynamic response to chronic anemia. Circulation, 39: 503-515.
11. Baldini, M., A. Marcon, R. Cassin, F.M. Ulivieri, D. Spinelli, M.D. Cappellini and G. Graziadei, 2014. Beta-thalassaemia intermedia: Evaluation of endocrine and bone complications. BioMed. Res. Int., 2014: 1-5.
12. Barry, M., 1974. Liver iron concentration, stainable iron and total body storage iron. Gut, 15: 411-415.
13. Barry, M., D.M. Flynn, E.A. Letsky and R.A. Risdon, 1974. Long-term chelation therapy in thalassaemia major: Effect on liver iron concentration, liver histology and clinical progress. Br. Med. J., 2: 16-20.
14. Wood, J.C., C. Enriquez, N. Ghugre, M. O. Duessel and M. Agullar *et al*., 2005. Physiology and pathophysiology of iron cardiomyopathy in thalassemia. Ann. New York Acad. Sci., 1054: 386-395.