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Role of Deferasirox as Iron Chelator and Its Side Effects in Thalassemic Children

Dr. Garima Mehta[1], Dr. Bela H.Shah[2], Dr. Dhara Gosai[3*], Dr. Rupal Kashiyani[4]

[1]Senior Resident, Department of Paediatrics, B.J. Medical College, Ahmedabad.
Email: garigmcs@gmail.com, Orcid Id: 0000-0002-0128-7117
[2]Professor and Head of Unit, Department of Paediatrics, B.J. Medical College, Ahmedabad.
Email: bela_dr@yahoo.co.in, Orcid Id: 0000-0002-5909-0237
[3]Assistant Professor, Department of Pediatrics, BJ medical college, civil hospital, Ahmedabad.
Email: drdharagosai@yahoo.co.in, Orcid Id: 0000-0001-9678-2868
*Corresponding author
[4]Second Year Resident, Department of Paediatrics, B.J. Medical College, Ahmedabad.
Email: rupalkashiyani@gmail.com, Orcid Id: 0000-0003-2254-6461.

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Abstract

Background: Thalassemia is most common haemoglobinopathy in India. Regular blood transfusion eliminate the complications of anaemia and compensatory bone marrow expansion. In parallel, transfusions result in a "second disease" -inexorable accumulation of tissue iron that without treatment is fatal in second decade of life. Iron accumulation is causing heart failure, cirrhosis, liver cancer, growth retardation and multiple endocrine abnormalities. **Objectives:** To study clinico-epidemiology and to observe prognosis and outcome in Thalassemic children on Deferasirox therapy.2.To analyze at what age and ferririn level Deferasirox started.3. To study quantum of whole blood tranfusion required at starting of Deferasirox therapy. **Methods:** present study was hospital based prospective analytical study conducted in 1.5 year in 1-12 years aged children, diagnosed with thalassemia (by history, examination, investigation and confirmation by Hb electrophoresis) and attends thalassemia clinic regularly, were put on deferasirox chelation therapy on basis of serum ferritin level and number of blood transfusion received. **Results:** Thalassemia incidence was higher in male, 6-9 year age, presenting age between 6 months- 1 year,Most common clinical feature found was pallor, Hepatomegaly and Spleenomegaly was most common sign of iron overload, Chelation therapy started at average 2.5 years age, Ferritin level at which deferasirox started was >1000ng/ml. Efficacy of deferasirox as a chelator agent had good response on lowering S. ferritin levels. Most common side effect of deferasirox found was increase in S. creatinin and GI disturbances. **Conclusion:** Children having Thalassemia major need regular blood transfusion and chelation therapy lifelong. Better treatment, monitoring and regular follow up had increase the life span of Thalassemic children to 3rd- 4th decade.

Keyword: Thalassemia, Deferasirox

INTRODUCTION

Thalassemia are a group of blood disorders with worldwide annual incidence of 1 in 100000. It is also the most common haemoglobinopathy in India with the incidence of around 3-4%. Thalassemia is characterized by decreased synthesis of one of the two main globin chains alpha and beta globin , that are needed for the formation of normal adult hemoglobin tetramer (consisting of two alpha and two beta globin chains). If beta globin

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chain synthesis is decreased or defective beta thalassemia results. The spectrum of beta thalassemia comprises of 1) Beta thalassemia trait/minor 2.)Beta thalassemia intermedia 3.)Beta thalassemia major

Regular red blood cells transfusion eliminate the complications of anaemia and compensatory bone marrow expansion, permit normal development throughout childhood, and extend survival. In parallel, transfusions result in a "second disease" while treating the first, that of inexorable accumulation of tissue iron, that without treatment, is fatal in the second decade of life . As there is no regulated mechanism for the excretion of excess iron, patients who require frequent blood transfusions inexorably develop chronic iron overload. Each unit of transfused red blood cells introduces 200–250 mg of elemental iron, with iron overload occurring after approximately ten to 20 transfusions. Iron accumulation is toxic to many tissues, causing heart failure, cirrhosis, liver cancer, growth retardation and mustiple endocrine abnormalities. Deferasirox is a once a daily oral iron chelator with established dose dependent efficacy in both adults and paediatric patients with transfusional iron overload. Deferasirox has also demonstrated the ability to remove cardiac iron and prevent future iron accumulation .Recent study is conducted to study the clinico-epidemiology of thalassemia and managment in Thalassemic children by regular blood transfusion and use of Deferasirox as chelating agent for the managing iron overload and its side effects in these children.

MATERIALS

- Study Design : Prospective and analytical study
- Study Period: From March 2018 to September 2019
- Study site: At a day care centre of Thalassemia in Tertiary care centre.
- **Patient Selection:**

1. Inclusion criteria:

- All patients who were diagnosed as thalassemia major in our institute and who attend thalassemia day care clinic regularly were included in my study.
- Age group 1 to 12 years which were put on oral iron chelating agent- deferasirox if needed according to guidelines.
- Patients coming for regular follow up over the period of my study and compliant to chelating therapy.

2. Exclusion criteria:

- Patients of sickle thalassemia, hemoglobin E disease, thalassemia intermedia and other thalassemia syndromes were excluded.
- Age <1 year and > 12 years were also excluded.

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METHODOLOGY

- Complete history and physical examination was done as mentioned in proforma further in all patients enroll in this study .Clinical presentation at the time of diagnosis of thalassemia major as well as those of iron overload were looked into separately.
- All the patients were diagnosed using hemoglobin electrophoresis.
- Past history specially regarding age of diagnosis, 1st blood transfusion taken, requirement of blood transfusion per year and their complication, time of starting oral iron chelating agent-deferasirox and its adverse effect, all of these were taken into consideration.
- Detailed systemic examination was done. Growth and development parameters including pubertal assessment were also taken in detail to study the effect of disease on the growth. Anthropometry was taken every 6 monthly.
- Moderate transfusion regimen was practiced where the pre transfusion hemoglobin was maintained between 9 - 10 gm/dl as it gives a near physiological oxygenation.
- All the patients in my study were transfused with leucodepleted ABO and Rh (D) compatible packed red blood cells after screening of transfusion transmitted infections like hepatitis B, hepatitis C, HIV, malaria, syphilis etc.
- Each patient was given a chart with accurate documentation of transfusion requirements, blood bank antibody monitoring, and transfusion reactions.
- Volume per transfusion usually given was 10-15 ml/kg administered over three to four hours.
- Serial monitoring of serum ferritin as a marker of iron overload was done in all patients every 3 monthly to monitor the efficacy of iron chelation.
- Renal function tests as well as liver function tests along with hepatitis B, C and HIV were done six monthly.
- Chelation therapy with deferasirox was started when (whichever was earlier)
    - Serum ferritin persistently > 1000 ng/ml
    - When 15 transfusions have been given given
- All patients needing chelation therapy were started on deferasirox. Initial dose was 20mg/kg and increased upto 45mg/kg as per requirement.

RESULTS & DISCUSSION

Proportion of Thalassemic children in this study is 1.4%. Out of which 91.6 % patients are on Deferasirox therapy.

Mean prevalence in India is 3.3%[6] .
In our study maximum patients belong to age group of 6 to 9 years with sex ratio of 1.43: 1 with male predominance (92%) who were on Deferasirox therapy.

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The diagnosis of thalassemia major was uncommon before 6 months but on the basis of positive family history and symptomatology they were suspected and confirmed by HbA2 levels by electrophoresis.

Majority of patients present between 6 months and 1 year as per the disease profile.

Table 1: Clinical Features at Time of Diagnosis (+ was not mentioned in previous studies)

	No. of patients	[7]Trehan and Sharma et al	[8]Nitin et al
Pallor	140 (98.5%)	99%	97.8%
Fever	102 (71.8%)	16%	18.6%
Irritablity	92 (64.7%)	+	+
Jaundice	7(4.9%)	5%	+
Feedings difficulties	58 (40.8%)	+	+
Failure to thrive	54 (38.0%)	30.7%	+
Hepatomegaly/ splenomegaly	30 (21.1%	22.7%	87.1%

In our study most common presenting features were pallor (98.5%) followed by fever (71.8%) and irritability (64.7%).

Pallor occurs as a result of ineffective erythropoiesis, increased hemolysis and an overall hemoglobin inadequacy.

Seroprevalence Of Transfusion Transmitted infection.[9]

In our present study none of them were detected of having HIV, only one patient was found to have hepatitis B(0.7%). while 15 patients (10.56%) were positive for anti-HCV antibodies.

HCV infection has gained importance as one of the major complication in multiple transfused patients during last two decades. The prevalence rate of seropositivity increases with the numbers of transfusion. This post-transfusion hepatitis has significantly contributed to the morbidity in thalassemia. It has been found that HCV hepatitis is more threatening than HBV hepatitis due to a greater risk of developing chronicity of liver diseases.

Table 2: Signs and Symptom of Iron Overload:

Signs/symptoms	No. of patients	[12]Girinath et al	[13]De sanctis et al
Hepatomegaly	109 (76.7%)	88%	+
Splenomegaly	104(73.2%)	82%	+

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Skin pigmentation	59(41.5%)	36%	+
Thalassemic facies	43(30.2%)	74%	+
Growth retardation	34(23.9%)	+	35%

In our study clinical evaluation regarding iron overload revealed hepatomegaly in 76.7% and splenomegaly in 73.2%.
Skin pigmentation was due to iron deposition in skin seen in 41.5% of the patients.

Most of the patients round 89.6% were started with deferasirox therapy at age of 1-3year as per the guidelines ferritin > 1000 ug/dL and transfusions more than 15 require chelation.
Mean age of starting iron chelation is 2.5 years.

Table 3: Efficacy Of Deferasirox as a Chelator Agent: By Relative Change in Ferritin Levels

	Response to ferritin after 6 months	[14]**Porter et al**
Good response	104(73.2%)	72.7%
No response	20(14.0%)	+
Poor response	18(12.6%)	27.3%

P value is 0.00002 considered significant. (Two tailed p <0.05 was considered statistically significant association).
GOOD RESPONSE: If two readings of ferritin i.e. in 6 months are in reducing trend then it was consider as good response and in these patients further dose titration was done by further monitoring.

NO RESPONSE: If two readings of ferritin are almost same then it was consider no response and dose was step up in 6 months.
POOR RESPONSE: If at 3 months ferritin levels increases it was considered as poor response and in these patients dose of deferasirox is increased at 3 months.

Table 4: Side Effects of Deferasirox

	Adverse effects	No. of patients	Percentage	[16]Cappellini et al	[15]Vallejo et al
1.)	**Increase in creatinine levels**	38	26.7%	38%	36.7%
2.)	**GI disturbances**	36	25.3%	15.2%	+
3.)	**Increase in SGPT levels**	19	13.3%	+	+
4.)	**Rashes**	13	9.1%	10.8%	+

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The most common deferasirox related adverse effects were increase in serum creatinine levels (26.7%) followed by related transient gastrointestinal disturbances that included abdominal pain, nausea and vomiting, diarrhea, and constipation (25.3%). These increase in serum creatinine was mostly transient and was noticed in routine follow up investigations and was generally within the normal range and they never exceeded 2 times of upper limit.

CONCLUSION

Thalassemia is inherited blood disorder in which the body makes abnormal hemoglobin which is usually diagnosed by severe pallor. It is mainly diagnosed at age between 6 months to 1year.Males are predominantly affected .As it is autosomal recessive disease, community with consanguinity are more affected like Muslims and then Sindhis. Average pre transfusion Hb was kept between 9-11 gm/dL .As the age increases, number of blood transfusion also increases and so the ferritin level. Growth parameters like weight and height are affected in Thalassemic children .Splenectomy is important treatment modality in controlling iron overload as number of blood transfusion decreases after splenectomy. Due to multiple transfusion some children were found seropositive for HCV and HBs Ag. After starting chelation therapy, most of the patients had good response and their ferritin level decreased .Thalassemia major is high burden disease. Children having Thalassemia major need regular blood transfusion and chelation therapy lifelong. There are now various newer chelators available which give better outcome. Better treatment, monitoring and regular follow up had increase the life span of Thalassemic children to 3rd- 4th decade .Child born with Thalassemia disease face long term problems like delayed growth and development , cognitive dysfunction and various endocrine abnormalities which can be dealt with proper chelation so to improve lifestyle of the person till he/she survive. Thalassemia is a preventable genetic disease and as said prevention is better than cure, the high risk population should know their status to prevent to Thalassemia major in next generation. If not early prenatal diagnosis in first trimester can give option of medical termination. The curative option of stem cell transplantation is available through costly.

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