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Original Article

Comparison of Efficacy of Oral Iron Chelators with Parenteral Chelators in Patients of B Thalassaemia Major

Masooma Shaheen[1], Maryam Habib[2], Wardah Aslam[3] and Mobina Ahsan Dodhy[4]

[1]Excel Laboratories Islamabad, [2]Department of Pathology, Shifa College of Medicine (STMU), [3]NORI Hospital Islamabad, [4] Department of Pathology, Rawalpindi Medical College (RMU).

ABSTRACT

Introduction: Transfusional hemosiderosis is a frequent complication seen in patients with Beta thalassemia major (β thalassemia major). They require regular iron chelation to get rid of excessive iron deposited in different organs of body. It is the need of the hour to find an appropriate iron chelator which can effectively chelate iron and improve the quality of life of these patients.

Objective: The aim of this study is to compare efficacy of parenteral iron chelator Desferrioxamine with oral iron chelator Deferasirox in patients of β Thalassemia Major.

Materials and Methods: I04 β Thalassemia major patients were randomly divided into 2 groups. Group 1 received parenteral iron chelator and Group 2 received oral iron chelator for one year. Serum ferritin levels were measured at start of study and then 3 monthly for 1 year.

Results: Group 1 had 36 (69.2%) males and 16(30.8%) females , Group 2 had 31(59.6%) males and21(40.4%) females. In Group 1 mean Serum Ferritin at 0 month was 3137.75 µg/l (± 1426.06) and at 12 month was 3180.00 µg/l (±1193.61) with difference in Serum Ferritin level from base line of 87.63µg/l (±1370.95). In Group 2 mean Serum Ferritin at 0 month was 2821.77µg/l (±736.51) and at 12 month was 2043.08 µg/l (±863.69) with difference in mean serum ferritin of 759.65 µg/l (±1099.74). Paired t-test was applied to compare means at base line and at 12-month follow-up which showed significant mean predicted improvement from baseline with p value of 0. 008.

Conclusion: Oral iron chelators, produce a greater reduction in serum ferritin levels as compared to parenteral iron chelators.

Key words: Beta Thalassemia, Chelating agents, Genetic Disease, Hemoglobinopathies.

Introduction

Iron remains of the most important and essential elements of numerous biological processes in the body. Iron regulation is a tightly controlled process in which iron is mostly found in bound form. Free or unbound iron can result in formation of reactive oxygen species which are highly toxic for the body. Iron overload can either be inherited genetically, or it can be acquired. Frequent blood transfusions are an important cause of iron overload[1,2]. Iron chelators form soluble complexes with iron and help in its removal from body. Many iron chelating agents have been developed and used in the past either alone or in combination with other therapies. Beta Thalassemia's are a heterogeneous group of genetic disorders that result from reduced or absent synthesis of β chains[3].

CORRESPONDENCE AUTHOR

Dr.Maryam Habib,

Assistant Professor Pathology, Shifa college of Medicine (STMU)

E-mail: maryam.scm@stmu.edu.pk

Phone: 03335966146

It is common around Mediterranean, Indian subcontinent and Southeast Asia[4]. It is a major health problem in Pakistan with an estimated carrier rate of 5%. These patients are managed with regular blood transfusions, 2-3 units every 4-6 weeks[4,5]. Regular blood transfusions lead to deposition of iron in tissues like heart, liver and endocrine organs[6]. Iron status in these tissues can be assessed by serum ferritin levels and other investigations like liver biopsy, CT scan, MRI, SQUID, and cardiac MRI. Serum Ferritin has prognostic significance, sustained levels of >2500µg/l are associated with increased risk of cardiac toxicity and death[7]. Management of trans fusional iron overload in Beta Thalassemia Major consists of chelation therapy with iron chelators. They are available in different formulations and can be divided into three main forms hexadentate, bidentate and tridentate form [8]. The most common side effects seen with these agents include ophthalmic and auditory reactions, GI disturbances, renal and liver failure The three iron chelators that are used most frequently in

patients of beta thalassemia major are desferrioxamine, deferiprone and deferasirox [9]. Desferrioxamine is a parenteral iron chelator, chelates iron from tissues and excretes mainly in urine and one third in stools. Life expectancy of thalassemia major patients on regular blood transfusions receiving desferrioxamine improves considerably. However, lack of compliance is frequent because of daily administration by infusion pump, and this hinders iron chelation. Deferasirox is a relatively new oral iron chelator approved for treatment of chronic iron overload due to blood transfusion in patients 2 years of age and older. It has high specificity for iron and is shown to have better efficacy to desferrioxamine at high doses regarding reduction in liver iron concentration and serum ferritin levels. It is also able to remove cardiac iron. Adherence with deferasirox has been proved to be better than desferrioxamine. Patient satisfaction and convenience with this drug are also better than with desferrioxamine[10, 11, 12]. This study is conducted on Pakistani population comparing efficacy of deferasirox versus desferrioxamine. It is anticipated that my study might help the patients suffering from β Thalassemia major improve their compliance with oral chelating drug i.e Deferasirox and hence their quality of life. Deferasirox may replace desferrioxamine in the long run for chelating iron based on its better iron chelating ability.

Materials & Methods

This comparative cross-sectional study was conducted at Benazir Bhutto Hospital and was completed in 20 months. 104 patients of β Thalassemia major were randomly enrolled in the study after receiving an informed consent from parents /guardian. They were randomly divided into two groups. GROUP 1 received parenteral iron chelator at a dose of 20-40mg/kg subcutaneously five days/week. GROUP 2 received oral iron chelator at a dose of 20-30 mg/kg /day. After patient consent and reassurance 5 ml of blood was collected by aseptic technique and serum extracted for performing serum ferritin levels in the Chemical laboratory Serum ferritin levels were measured by a solid phase, two site, chemiluminescent immunometric assay called as IMMULITE/IMMULITE 1000 ferritin. These serum ferritin levels were taken as base line levels and patients were randomly selected for the type of iron chelation therapy. Serum ferritin levels were subsequently measured at 3,6,9 and 12 months interval. All the collected data was entered in Statistical Package for Social Sciences (SPSS) version 23. Analytical variables included numerical data for age, age at first transfusion, number of previous transfusions, serum ferritin levels at 0,3,6,9 and 12months for which mean, median, standard deviation was calculated. Serum ferritin levels in two groups were compared with each other. However, efficacy of drug was found by comparing mean serum ferritin level at o month and 12 months in Group1 and 2.

Percentage was used for qualitative data like gender. Paired sample T- test was used to determine the greater difference in serum ferritin levels between two groups. After the application of test of significance, the calculated P-value was calculated as < 0.05 which was taken as significant.

Results

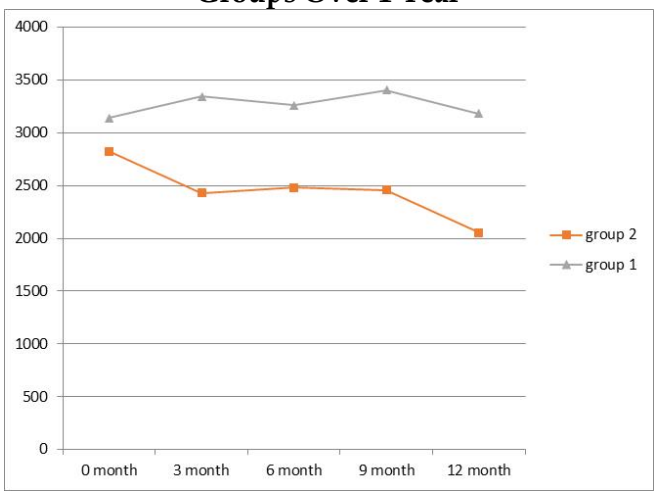
Out of 104 patients enrolled in the study all patients completed the study. Age and gender distribution of patients in two groups is shown in Table No 1 .

Table No-1: Patient Demographic Data

Variable	Group 1	Group 2
AGE (*YEARS*)		
Range	2-12	2-8
Mean	5.69 (±2.24)	3.79 (±1.41)
SEX %		
Male	36(69.2%)	31(59.6%)
Female	16(30.8%)	21(40.4%)
AGE AT FIRST TRANSFUSION (MONTHS)		
Range	2-9	3-10
Mean	4.81 (±2.19)	6.56 (±1.93)
TOTAL No OF TRANSFUSIONS		
Range	15-147	14-94
Mean	62.96 (±28.30)	38.29 (±17.59)
MEAN FALL IN S.FERRITIN µg/L at the end of study	87.63 (±1370.95)	759.65 (±1099.74)

Distribution of values of serum Ferritin at 0 months and at 12 months in both the groups is shown in Figure 1.

Figure 1: Mean Serum Ferritin Levels in Both Groups Over 1 Year



GROUP 1: Parenteral Group
GROUP 2: Oral Group

Paired t-test was applied to compare means at base line and at 12-months serum ferritin follow-up as shown in Table No 2:

TABLE No 2: Mean and P-Value of Serum Ferritin in Group-1 And Group

Variable	Mean value				P value at 12 weeks
	At 0 month		At 12 months		
	Group 1	Group 2	Group 1	Group 2	
Serum ferritin mean±SD	3137.75 ±1426.06	2821.77 ±763.51	3180.00 ±1193.61	2043.08 ±863.69	0.008

GROUP 1: Parenteral Group
GROUP 2: Oral Group

Discussion

β-Thalassemia major is a recessively inherited anemia in which the newborn will have a near total inability to produce β globin chains, leading to deficiency in synthesis of hemoglobin. Children will develop severe anemia if left untreated. Treatment by regular blood transfusions reverses these pathological mechanisms. With each transfusion iron is deposited in body causing complications[13,14,15]. Treatment by regular blood transfusions reverses these pathological mechanisms. With each transfusion iron is deposited in body causing complications. Patients are given iron chelation therapy to treat iron overload.

Desferrioxamine is a parenteral iron chelator which has been in use for 40 years. Unfortunately, adherence to treatment is suboptimal particularly in adolescents and young adults due to challenges of administering it in slow subcutaneous or intravenous infusion over 8-12 hours 5-7 nights per week. As many as one third of the patients are noncompliant to treatment. Nonadherence to therapy can be a major factor leading to death in patients.

Deferasirox (Exjade) is a relatively recently introduced oral iron chelator, given once daily as oral suspension in a dose of 10-30 mg/kg. This drug has been used in various clinical trials for its iron chelating ability and has been compared with parenteral chelators. Previous studies in adult patients with beta thalassemia major have revealed that treatment with this drug could substantially remove iron from body[16,17].

A study was conducted by Muhammad W eta al[18] in Peshawar on 108 patients of Beta thalassemia Major patients .They took equal number of male and female patients as compared to our study in which we enrolled 104 patients of Beta thalassemia Major out of which there were 67 males and 37 females. In their study highest serum Ferritin level was observed at 12 years of age with serum ferritin level of 8160.5ng/ml in males and 13,349.5 mean serum ferritin levels in females at age of 17 years, in contrast to our study in which we studied the baseline serum ferritin and then compared it at 12 months .Another study was done by Shah S eta al[19] on 100 of Beta thalassemia major patients with gender distribution of 53 % males and 47 % females. Similarly in our study there were 64.4 % males and 35.5% females. A study conducted by Pinto WM et al[20] showed that deferasirox was a better iron chelator than desferrioxamine in terms of compliance and effects on iron chelation. The results are comparable to our study which revealed deferasirox was better at chelating iron as compared to desferrioxamine when mean serum ferritin levels were compared at baseline and after 12 months of therapy.

Moukalled NM[21] et al conducted two trials comparing efficacy of deferasirox in transfusion dependent and non-transfusion dependent beta thalassemia patients. They demonstrated that the patients after treatment with deferasirox had significant reduction in liver iron as compared to those patients which were treated with desferrioxamine. In our study we demonstrated that deferasirox had significant impact on reduction of serum ferritin levels in both male and female group as compared to treatment with desferrioxamine. Similarly, a study was conducted by Yang G[22] et al on Chinese patients suffering from Beta thalassemia major. They found deferasirox was better at reducing serum ferritin and liver iron as compared to

desferrioxamine which had better results in terms of chelating cardiac iron. Our study also had comparable results and proved that deferasirox was better at reducing serum ferritin as compared to desferrioxamine.

Conclusion

Conclusion of the study is that the oral iron chelator (DEFERASIROX) is more efficacious as compared to parenteral iron chelator (DESFERRIOXAMINE).

Limitations of Study: Despite being an effective, this study has certain limitations. The time duration of study was small, and age of patients could not be reduced from < 2 years as deferasirox is effective only at ages > 2 years. This study provides food for thought and encourages other studies establishing efficacy of deferasirox in younger children and over longer duration of time.

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Conflicts of Interest: No conflict of interest to declare

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CONTRIBUTION OF AUTHORS	
Author	**Contribution**
Dr.Masooma Shaheen	A,B,C
Dr. Maryam Habib	A,B,C
Dr. Wardah Aslam	A,C
Dr.Mobina Ahsan Dodhy	A,C

KEY FOR CONTRIBUTION OF AUTHORS:

A. Conception/Study/Designing/Planning
B. Active Participation in Active Methodology
C. Interpretation/ Analysis and Discussion