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ORIGINAL ARTICLE

# EFFECT OF DIFFERENT MODALITIES OF CHELATION IN BETA THALASSEMIA

KUMAR P*, GHALAUT V S**, ABROL P***, SEN J****,SACHDEVA A*****

**Abstract**

Beta-thalassemia major is a genetic blood disorder that results in defective production of haemoglobin.In India, almost 25 million people are carriers of beta-Thalassemia gene. Beta Thalassemia affects almost all body organ systemsand the main stay of treatment is regular blood transfusion which has its associated complications, the most important being iron overload.The iron chelators have a major role improving the life expectancy of the patients. Desferrioxamine and Deferiprone are two such chelating agents being used in patients on blood transfusion. **Methods**: We carried out a study on 45 Thalassemics receiving blood transfusion and divided them into three groups on the basis of iron chelators used. Their cardiac and hepatic status was assessed and correlated with serum ferretin levels that had been on chelation therapy for a minimum of six months. **Results:** The serum ferretin did not show a significant change in all three groups but the patients on combination therapy showed improvement in cardiac and hepatic functions. **Conclusion:** Although promising, a longer duration of study on a larger number of patients is required to assess the beneficial effect of combination therapy over individual chelators.

**Keywords:** Beta thalassemia, serum ferritin, Deferiprone, Desferrioxamine

*( MD)(paediatrics), **(MD) (Biochemistry), ***(MD) (Paediatrics), ****(MD)( Radiology), *****(MD) (Biochemistry), PGIMS Rohtak,Haryana,(India)
**Corresponding Author:**
Dr. Ashuma Sachdeva ,1214 Sector -1,HUDA, Rohtak-124001, Haryana, India.
ashuma@in.com

## Introduction:

Thalassemias are a group of hetero-geneous disorders, recessively inherited, resulting from various mutations of a single gene which codes for globin chains of Hb, leading to reduced or absent synthesis of globin chain. and the prevalence rate varies from 1-17%, in different regions, with a mean prevalence of 3.3%. Over 9000 thalassemic children are born every year in India[1]

Beta Thalassemia affects almost all body organ systems. These effects are due to ineffective erythropoiesis, expanded medullary spaces, extra-medullary erythropoiesis and a huge caloric need. Anaemia, cellular level hypoxia and increased iron absorption lead to further complications[2]. Iron overload of tissues, which is fatal with or without transfusion, if not prevented or treated, is the most important complication of beta-thalassemia. After approximately one year of transfusions, iron begins to deposit in parenchymal tissues [3]. In the absence of chelation therapy, the accumulation of iron results in progressive dysfunction of heart, liver and endocrine glands.

The mainstay of treatment of severe Thalassemia is regular blood (packed cells) transfusionThe major complications of blood transfusion are those related to transmission of infectious agents or development of iron

overload. As iron accumulates and exceeds body needs, production of apoferritin is accelerated to provide means for storing iron in non-toxic forms such as ferritin or hemosiderin. But, the excessive iron in the free pool is responsible for peroxidation of cell membrane components, which is the major cause of organ damage from excessive iron [4].

. The introduction of chelating agents capable of removing excessive iron from the body has increased life expectancy of these patients. Desferrioxamine and Deferiprone are two such chelating agents being used in patients on blood transfusion. When administered in conjunction with blood transfusion regimens, chelation is able to delay the onsets of cardiac diseases and in some patients even prevent its occurrence. High dose of Desferrioxamine has been reported to achieve some benefits even in patients with massively elevated hep,atic iron concentration [5]. Recent clinical trials have suggested that using Desferrioxamine in combination with Deferiprone increases the quantity of iron excreted from the body, in heavily iron overloaded patients, because each drug removes iron from different parts of the body [6]. Hence, the combination therapy may have a dual rationale- increasing total iron excretion and taking advantage of organ selectivity.

## Materials And Methods

The study was done for a period of one year, in the department of Paediatrics and Biochemistry at Pt. B.D. Sharma PGIMS Rohtak, Haryana, India, on 45 patients who were divided into three groups, depending on the chelation therapy used.

## Inclusion Criteria

1. Patients should have received more than 20 blood transfusions.
2. Patients with serum ferritin levels more than 1000ng/ml.
3. On chelation therapy for a minimum of 6 months on the same drug.
4. Informed consent taken from all the patients/ guardians before allocating the patient to a particular group.

## Exclusion Criteria

1. Children with poor compliance.
2. Children who could not be followed.
3. Terminally ill patients.

## Method Of Study

**GROUP-I:** This group included 15 children receiving oral iron chelator Deferiprone 75mg/kg/day in 3 divided doses] daily.

**GROUP-II:** This group included 15 children receiving subcutaneous Desferrioxamine injection at a dose of 40 mg/kg/day over 8-10 hrs in the night for five days a week .

**GROUP-III:** This group included 15 children getting regular oral Deferiprone 75mg/kg/day daily in three divided doses and subcutaneous Desferrioxamine 40mg/kg/day over 8-10 hrs for two days a week.

A detailed history, clinical examination, routine investigations and anthropometric evaluation was done on all the patients and physical examination of all the systems was done thoroughly.
The assessment of cardiac system was done by M-mode echo-cardiography using phased array sector scanners with a frequency of 2.5 to 6 MHz transducer.

Serum ferritin levels were estimated by chemiluminescence method done on ADVIA CENTAUR CP system.

All the parameters and investigations were reviewed after one year interval, and the study was interpreted under following headings:-

- Any correlation, if present, between serum ferritin and cardiac and liver status.
- Serum ferritin and liver function tests were done at quarterly intervals
- HIV and HbsAg were done at the start and end of the study.

Results were compared in all the three groups and were analysed using Student's t-test (Paired and Unpaired)

## Observations And Results

**(Table/Fig-1) Serum ferritin level of three groups (ng/ml). Mean levels of serum ferritin were not significant statistically (p>0.05)in either of the three groups.**

| GROUP | 1 | 11 | 111 |
|---|---|---|---|
| | MEAN ± SD | MEAN ± SD | MEAN ± SD |
| Initial | 4475.26±1950.56 | 4880.4±3355.89 | 4036.26±3004.53 |
| At 3 Months | 4876.26±2302.42 | 4705.46±2297.34 | 4004.6±2242.47 |
| At 6 Months | 4622.73±1631.4 | 4880.26±2492.20 | 4087.2±2192.09 |
| At 9 Months | 4516.6±1818.75 | 4557.53±2067.65 | 4086.2±2644.68 |
| At 12 Months | 4459.73±1555.28 | 4498±2366.96 | 4112.06±2261.85 |

**(Table/Fig 2) Mean values of Liver Enzymes of three groups**

| GROUP | I | | | II | | | III | | |
|---|---|---|---|---|---|---|---|---|---|
| | SGOT U/L | SGPT U/L | ALP U/L | SGOT U/L | SGPT U/L | ALP U/L | SGOT U/L | SGPT U/L | ALP U/L |
| Initial | 126.2 ±69.3 | 156.33 ±99.8 | 377.6 ±148.91 | 111.93 ±45.69 | 117.06 ±33.99 | 317.13 ±96.65 | 99.53 ±63.81 | 103.93 ±61.67 | 309.6 ±86.7 |
| At 3 Months | 119.13 ±61.16 | 134.26 ±65.11 | 356.06 ±119.07 | 109.86 ±42.74 | 116.13 ±25.34 | 294.46 ±58.18 | 102.64 ±63.43 | 100.66 ±57.24 | 295.1 ±67.1 |
| At 6 Months | 121.4 ±75.01 | 125.33 ±69.89 | 353.93 ±118.18 | 105.86 ±28.61 | 116.53 ±25.34 | 309.66 ±70.15 | 106.6 ±59.15 | 98.06 ±49.81 | 306.2 ±59.9 |
| At 9 Months | 111.6 ±55.45 | 136.66 ±58.06 | 367.86 ±117.32 | 104.66 ±26.28 | 113.86 ±18.44 | 301.6 ±57.96 | 104 ±74.4 | 101 ±46.54 | 297.3 ±59.3 |
| At 12 Months | 128.73 ±70.39 | 144.2 ±74.49 | 384.26 ±127.93 | 105.46 ±30.44 | 113.08 ±18.04 | 306.46 ±81.98 | 97.66 ±53.56 | 101.4 ±62.13 | 303 ±46.7 |

At the end of the study, mean levels of SGOT, SGPT and serum alkaline phosphatase were highest with Deferiprone therapy and were comparatively less raised with combination therapy. Mean levels of serum bilirubin were not significant statistically (p>0.05)in either of the three groups.

**(Table/Fig 3) Correlation of cardiothoracic (CT) ratio of thalassemic patients with serum ferritin at one year**

| CT RATIO | I (%) | II (%) | III (%) | S.FERRITIN |
|---|---|---|---|---|
| >0.55 | 0 | 7 | 0 | 8400 |
| 0.53-0.55 | 7 | 7 | 20 | 8114±1039.85 |
| 0.50-0.52 | 27 | 33 | 7 | 5247.3±1674.94 |
| <0.5 | 66 | 53 | 73 | 3272.55±954.36 |

**CT ratio was high in patients with high serum ferritin levels which was statistically significant (p<0.05)**

## Discussion

In our study, the mean age of group-I patients was significantly, less than in group II and group III patients .The reason for younger children not taking Desferrioxamine [group II and group III] can be attributed to fear for injection and difficult mode of administration, taking much longer time (8-10 hours) to deliver the drug.

The anthropometric assessment of the subjects included in our study indicated growth retardation. The height of 56% of patients and the weight of 49% of patients was below 3rd-centile for their age and sex when compared with CDC-2000 standard, indicating profound growth retardation among thalassemics. The weight and height of group-I patients was significantly, less than the patients of group II and group III, because in group I the patients were of comparatively younger age group than patients of group II and group III. Our findings correlate well with findings of a study by Karamifar et al[7] who evaluated puberty and linear growth in 146 beta-thalassemic major patients 984 males and 62 females) of age group 10-22 years. They found that, short stature was present in 62.9% of girls and 69% of boys of all age group. About 78.9% of girls above 12 years of age and 83.3% of boys above 14 years of age,, were less than 2 SD below mean for normal height. This suggests that height reduction is more with increasing age in thalassemic children. In our study, we also found that height reduction is more with increasing age. It was seen that in group I with mean age 9.63± 4.13 years, the height reduction was lesser with only 47% of children below 3rdcentile as per CDC-2000 standard, while in both group II (mean age 15.63±3.97 years)and group III (mean age 13.3±3.76 years) the height reduction is more with 60% children in each group being below 3rdcentile as per CDC-2000 standard.

In our study, serum ferritin levels showed a fall in both group I and group II, but in group III, it showed a rise [Table/Fig 1]. These findings were non-significant in all the three groups. A study by Gomber et al [8] has shown that Desferrioxamine was effective in reducing iron overload whereas, serum ferritin levels showed a rise in patients on Deferiprone and on combination regimen. The rise in serum ferritin concentration with Deferiprone has been attributed to rapid glucoronisation of the drug in the liver making it ineffective to chelate the stored iron in the body.

The hepatic status of all the groups was found to be deranged in our study. The level of liver enzymes was raised in all the groups. The

mean level of all the three liver enzymes studied (SGOT/SGPT, serum alkaline phosphatise) was found to be raised more in group I than in group II and the group III, but the difference was not statistically, significant($p>0.05$). Various studies have found that Desferrioxamine arrests progressive liver fibrosis even when taken in inadequate doses, as judged by reduction in liver iron concentration and improvement in liver function test. High doses of Desferrioxamine have been reported to achieve some benefits even in patients with massively elevated hepatic iron concentration [5].

ALT levels often rise in patients under Deferiprone treatment, usually during the initial months of treatment, and then stabilise or decrease after 3-6 months.

In chest X-ray, we found that CT ratio was not significantly different in all 3 groups. It was also found that CT ratio was higher with high mean serum ferritin level. In a study conducted on 24 patients of thalassemia major, Leon et al [9] found cardiomegaly in 50% of the patients. In our study, cardiomegaly was found in 36% of patients.

Combined chelation therapy with Desferrioxamine and Deferiprone reduced myocardial iron and improved cardiac function in a study by Tanner[10].In our study, we also found improvement in cardiac functions in patients taking Deferiprone (group-I) and combination therapy(group-III), but the results were non significant. A large number of patients and longer duration of study is required to evaluate these criteria.

In a comparative study of iron chelators by Glickstein et al [11], it was found that the effect of Desferrioxamine at therapeutically relevant concentrations, was primarily by elimination of labile plasma iron while Deferiprone had effect on intracellular labile iron. The combination of a weak chelator which has a better ability to penetrate cells, with a stronger chelator that penetrates cells poorly but has a more efficient urinary excretion, results in a synergistic effect through iron shuttling between the two compounds. Such a "shuttle" was proposed by Grady[12] who found that the combination of these chelators resulted in total iron excretion 2.4 to 3.4 times higher than Desferrioxamine alone.

In our study, the same "shuttle" effect is probably responsible for better outcome of results in patients on combination regimen, though results are statistically insignificant. A longer duration of study on a larger number of patients could yield a significant data.

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