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*RESEARCH ARTICLE*

# TO STUDY EFFECTIVENESS OF DEFERASIROX, AN ORAL IRON CHELATOR IN BLOOD TRANSFUSION DEPENDENT PEDIATRIC THALASSEMIA PATIENTS

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## *Abstract*

**Background:** Inblood transfusion related thalassemia patients, high iron state is observed because of regular blood transfusion. Our body has limited mechanism to excrete iron, excess of iron gets deposited in various organs causing their dysfunction. To prevent the complication associated with this iron overload use of iron chelators becomes important in management of such patients.

**Aims /Objectives**: 1.To determine effectiveness of deferasirox, an oral iron chelator to decrease iron overload in reference to serum ferritin level in blood transfusion dependent pediatric thalassemia patients. 2.To determine effectiveness of deferasirox in reducing iron deposition induced organ damage.

**Methods:** This is a hospital based retrospective observationalstudy conducted on 80 blood transfusion dependent thalassemia patients admitted in tertiary care hospital. Data was collected in pre-designed case record sheets after taking consent from parents**.**

**Results:**in the present study the mean age was 7.12 years for females and 10.93 years for males. The mean of pre and post blood transfusion hemoglobin was significantly higher (7.07 and 10.76; respectively). The mean blood transfusion days are 26.33. Mean annual blood requirement is 198.99. Mean drop rate is 1.02. On comparing mean ferritin levels, there was a significant difference between baseline (711.81), start of deferasirox treatment (1271.71) and the end of 2$^{nd}$ dose increment of deferasirox (2076.11). The mean ferritin decreased significantly after starting deferasirox (from 1360.03 to 1271.71) by the end of1$^{st}$dose increment (from 1832.41 to 1696.75) by the end of 2$^{nd}$ dose increment (from 2097.32 to 2076.11) , but when we compare mean ferritin after end of 2$^{nd}$dose increment of deferasirox (2076.11) with6 month back mean ferritin (2506) or current mean ferritin (2514.90) there is increase in ferritin.Mean blood transfusions at start of deferasirox is (11.025), at 1$^{st}$ dose increment is (26.13), at 2$^{nd}$ dose increment is (42.12).There were no organ complications seen with the present population at the end of the study

**Conclusion**: from the results of our study, we state that using deferasirox as oral iron chelator in blood transfusion dependent pediatric thalassemia patients helps in reducing iron overload till we reach maximum dose of oral deferasirox but beyond that there is significant increase in serum ferritin level,thereby necessitating use of

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another iron chelator along with oral deferasirox(either deferoxamine, deferiprone or some new iron chelator),. Also in this study it is observed that there is no iron deposition related significant organ damage.



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## Introduction:-

Blood transfusion dependent thalassemia is a genetic disease characterized by a reduced ability to produce hemoglobin, which causes severe anemia that need regular blood transfusion to prevent growth,skeletal and neurological complication. This regular blood transfusion leads high iron state(1)(2)Each unit of transfused blood contain 200 to 250 mg of elemental iron. (2)Body has limited mechanism to excrete iron,thus development of iron overload in chronically blood transfused patients becomes inevitable. This iron gets deposited in various tissues and organs in body like heart, liver, pituitary etc causing organs dysfunction and complications. Here, mainstay of managing transfusion related iron overload is through using iron chelators. Iron chelators act by neutralizing unbound iron, which has 6 active sites. Iron chelators binds these active sites and causes inactivation of iron. Effectiveness of iron chelator also depends on other factors like compliance, associated infection, socioeconomic status. Commonly used iron chelators are deferoxamine(hexadentate), deferasirox(tridentate), deferiprone(bidentate) (2). Deferasirox is latest oral iron chelator with long half-life of upto 16 hour this helps in once a day administration(3) , also has mild adverse effects which makes it a preferred choice of iron chelator.

## Aims:-

To determine effectiveness of deferasirox, an oral iron chelator to decrease iron overload in reference to serum ferritin level in blood transfusion dependent pediatric thalassemia patients.

## Objectives:-

1. To determine effectiveness of, an oral iron deferasirox chelator to decrease iron overload in reference to serum ferritin level in blood transfusion dependent pediatric thalassemia patients.
2. To determine effectiveness of deferasirox in reducing iron deposition induced organ damage.

## Material And Methods:-

**Study design-**

This was a hospital based retrospective observational study.

**Study site-**

Conducted in a thalassemia unit tertiary care centre.

**Sample size-**

A sample of 80diagnosed cases of blood transfusion dependantpaediatric thalassemia, enrolled under thalassemia unit formed the study.

**Inclusion criteria:**

1. All diagnosed cases of blood transfusion dependent thalassemia patients enrolled under thalassemia unit at tertiary care center.
2. All patient who gave consent.

**Exclusion criteria**

1. Patients who are not yet started on oral iron chelator, deferasirox
2. Patients who didnot give consent
3. Patients not enrolled under thalassemia unit

**Procedure –**

Written informed consent taken from one of the parents. A total of 80 patients were enrolled in this study. Data extracted from case record sheets of patients under thalassemia unit which mainly included serum ferritin level at diagnosis, at start of treatment with deferasirox, after 1$^{st}$ and 2$^{nd}$ dose increment of deferasorix and after 6 months of

starting treatment,1st and 2nd dose increment. Data pre-processing and refining done in Microsoft excel sheet. Statistical analysis of the data and publication of result done.

**Statistical analysis –**

Primary data was collected in paper based proforma and the data was then coded and entered in Microsoft Excel spreadsheets 2019. Statistical analysis was done on SPSS 24.0. Categorical variables were taken in the form of frequencies and percentages. Distribution was represented by pie charts or bar graphs. Continuous variables were expressed in the descriptive statistics tables as means, standard deviation and range.All p values less than 0.05 was considered to b statistically significant. The data was checked for its normality of distribution using Shapiro Will Test and was found to be normally distributed. The continuous data of 2 observations were compared using a student t test. For more than 2 groups, ANOVA was applied followed by Tuckeys post Hoc test.

## Result:-

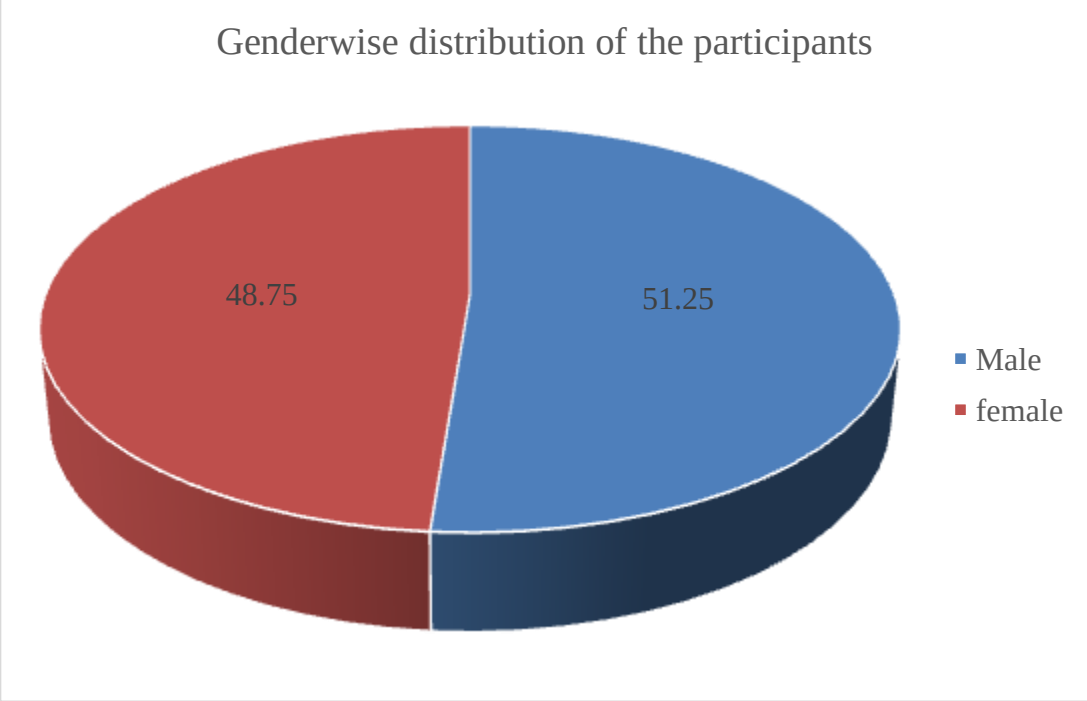
**Table:-**Mean age and gender:

| Gender | Mean age | Standard deviation |
|---|---|---|
| Female | 7.12 | 2.18 |
| Male | 10.93 | 3.30 |

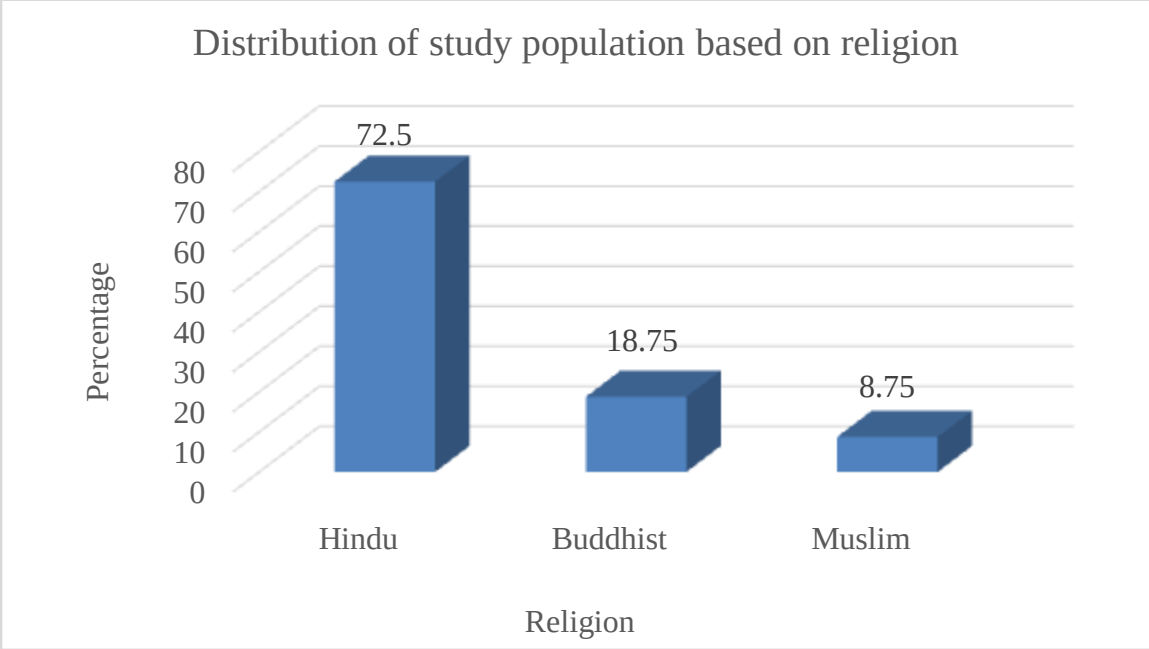
t-test p value-0.7440

The mean age of male kids was significantly more than that of females.

**Graph:-** Gender wise distribution of the study population:



**Graph:-**




Mean BMI-0.40±0.20

**Table:-** Mean of Pre and Post BT Hb:

| Hb | Mean | Standard deviation |
|---|---|---|
| Pre | 7.07 | 0.88 |
| Post | 10.76 | 0.81 |

Paired t-test p value-0.0000001
The mean of Post BT HB was significantly higher than that before the start of the therapy.

Mean of Blood Transfusion Every (in days)= 26.33±4.34
Mean ABR= 198.99±38.83
Mean Drop rate=1.02±0.27

**Table:-** Mean comparison of Ferritin across the timeline:

| Group name | Mean ferritin | Standard deviation |
|---|---|---|
| At diagnosis | 711.81 | 376.46 |
| Current ferritin | 2514.90 | 1151.16 |
| 6 month back | 2506 | 1076.98 |
| At start of deferasirox | 1360.03 | 287.35 |
| 6 months after start of deferasirox | 1271.71 | 267.22 |
| Start of 1$^{st}$dose increment | 1832.41 | 516.51 |
| 6 months after 1$^{st}$dose increment | 1696.75 | 452.40 |
| Start of 2$^{nd}$dose increment | 2097.32 | 491.92 |
| 6 month after 2$^{nd}$dose increment | 2076.11 | 464.29 |

ANOVA p value-0.1

Tukey's post hoc test:

| Group compared | P value | Interpretation |
|---|---|---|
| 6 months back vs Current Ferritin | 1.0 | No significant difference in mean ferritin levels |
| 6 months back vs Ferritin at diagnosis | 0.0000 | Mean Ferritin level at 6 months back significantly higher than that during diagnosis |
| 6 months back vs Start of therapy | 0.0000 | Mean Ferritin level at 6 months back significantly higher than that at the start of therapy |

| | | |
|---|---|---|
| 6 months back vs End of the first therapy | 0.0000 | Mean Ferritin level at 6 months back significantly higher than that at the end of base therapy |
| 6 months back vs start of 1st Increment | 0.0000 | Mean Ferritin level at 6 months back significantly higher than that at the start of 1st Increment |
| 6 months back vs end of 1st Increment | 0.0000 | Mean Ferritin level at 6 months back significantly higher than that at the end of 1st Increment |
| 6 months back vs start of 2nd increment | 0.0054 | Mean Ferritin level at 6 months back significantly higher than that at the start of 2nd increment |
| 6 months back vs end of 2nd increment | 0.0025 | Mean Ferritin level at 6 months back significantly higher than that at the end of 2nd increment |
| Current Ferritin vs Ferritin at diagnosis | 0.0000 | Mean Current Ferritin level was significantly higher than that at the diagnosis |
| Current Ferritin vs Start of therapy | 0.0000 | Mean Current Ferritin level was significantly higher than that at the start of therapy |

Mean blood transfusions:

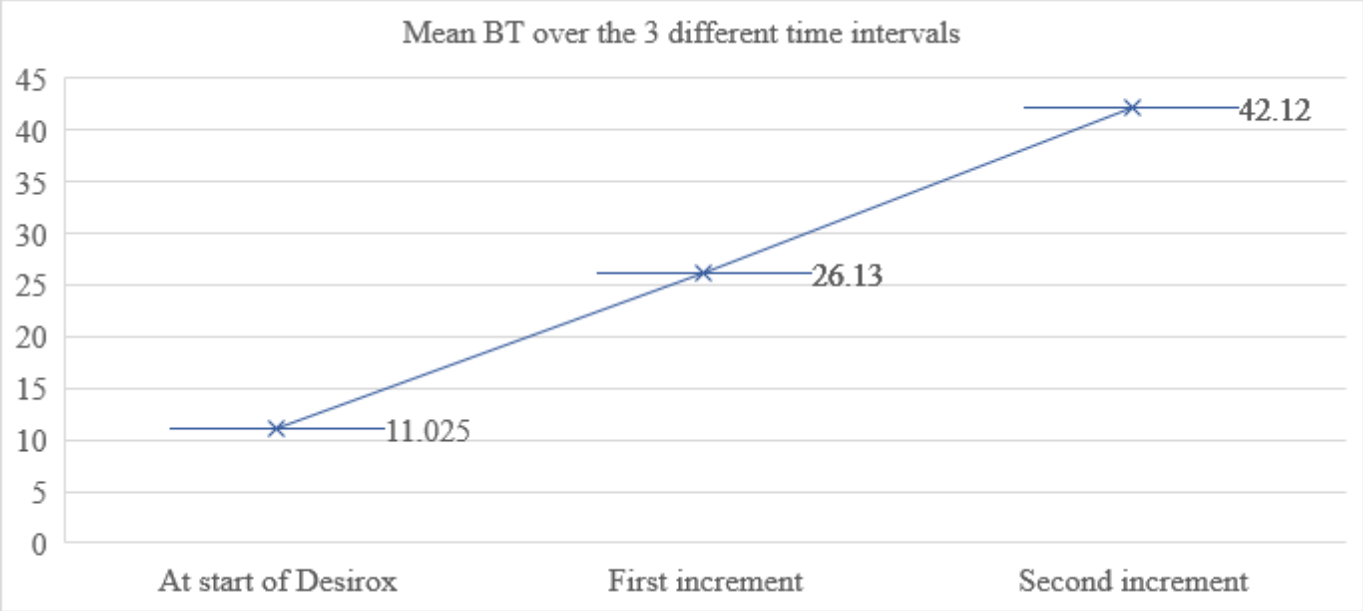
| Time line | Mean | Standard deviation |
|---|---|---|
| At start of deferasirox | 11.025 | 1.66 |
| Start of 1st dose increment | 26.13 | 3.53 |
| Start of 2nd dose increment | 42.12 | 4.94 |

On comparison of the groups using ANOVA, the F value was 1398.87

There was a significant difference in between the mean blood transfusion across the 3 different time intervals.

Tukey's post Hoc test:

| Time line | P value | Interpretation |
|---|---|---|
| At start of treatment v/s 1st dose increment | 0.00000 | The mean of BT at baseline was significantly lower than 1st increment |
| At start of treatment v/s 2nd dose increment | 0.00000 | The mean of BT at baseline was significantly lower than 2nd increment |
| 1st dose increment v/s 2nd increment | 0.00000 | The mean of BT at 1st increment was significantly lower than 2nd increment |




The results of the study have been tabulated above. 80blood transfusion dependent pediatric thalassemia patients were enrolled in this study. In the present study the mean age was 7.12 years for females and 10.93 years for males. The mean of pre and post blood transfusionhemoglobin was significantly higher (7.07 and 10.76; respectively). The mean blood transfusion days are 26.33. Mean annual blood requirement is 198.99. Mean drop rate is 1.02. On comparing mean ferritin levels, there was a significant difference between ferritin at diagnosis (711.81), start of treatment with deferasirox (1271.71) and the end of 2nd dose increment (2076.11). The mean ferritin decreased significantly after starting deferasirox (from 1360.03 to 1271.71) by the end 1stdose increment (from 1832.41 to 1696.75) by the end of 2nd dose increment (from 2097.32 to 2076.11) , but when we compare mean ferritin after end of 2nddose increment of deferasirox (2076.11) with 6 month back mean ferritin (2506) or current mean ferritin (2514.90) there is increase in ferritin. Mean blood transfusions at start of deferasirox is (11.025), at 1st dose increment is (26.13), at 2nd dose increment is (42.12).There were no organ complications seen with the present population at the end of the study

## Discussion:-

Our study is mainly based on evaluating the effectiveness of deferasirox in reducing iron overload in reference with serum ferritin level in pediatric thalassemia patients. These patients need regular blood transfusion for maintaining hemoglobin level, chronic blood transfusion leads to high iron status. Different iron chelators are being used in these patients to control iron over load and associated complications. Commonly used iron chelators are deferoxamine(hexadentate), deferasirox(tridentate), deferiprone(bidentate) (2). Deferasirox is latest oral iron chelator with long half-life of upto 16 hr this helps in once a day administration(3) , also has mild adverse effects which makes it a preferred choice of iron chelator.

Ali Aycicek et al. conducted a study on efficacy of deferasirox in children with B thalassemia, they concluded that deferasirox is well tolerated and require a dose of >30 mg\kg\day to reduce iron in regularly transfused pediatric patients(4). Also similar study conducted by Mohammadreza Rafati et al. on 80 patients with deferasirox concludes significant decrease in serum ferritin level after 6 months of treatment with deferasirox with dose of 30 mg\kg\day(5)

However, with increasing age and blood transfusions monotherapy becomes insufficient to control iron over load as we cannot increase dose of deferasirox beyond a limit. Chayamon Takprandit et al. conducted a study on 5 patients poorly responding to deferasirox monotherapy(40mg\kg\day) after a time and started on combination therapy with deferasirox and deferoxamine which showed significant decrease in serum ferritin level after 6 months of treatment(6). A similar study was conducted by Ashutosh Lal, John Porter et al on 22 thalassemia patients with persistent iron load on monotherapy, which then treated with combination therapy of deferasirox and deferoxamine concluded significant decrease in serum ferritin level after 1 year of treatment(9).

A study done by sidharth Totardi et al. using deferasirox and deferiprone as a combination treatment in 36 thalassemia major patients who are heavily iron loaded and monotherapy is not enough to reduce serum ferritin levels. At the end of 1 year of treatment concluded that there was significant decrease in serum ferritin level and iron over load(8).

It has been observed that treatment with oral iron chelator deferasirox causes significant decrease in serum ferritin level and iron over load. But after certain time monotherapy with iron chelator in these blood transfusion dependent thalassemia patients is not enough to decrease iron over load, demanding combination treatment with 2 iron chelators.

## Conclusion:-

Deferasirox is a good oral iron chelator, neutralises iron by inactivating binding site of unbound iron. In this study it is found that oral iron chelator deferasirox is effective in reducing iron overload which is evident in reference with decrease in serum ferritin level after starting the drug.The mean ferritin decreased significantly afterstarting deferasirox (from 1360.03 to 1271.71) by the end 1$^{st}$dose increment (from 1832.41 to 1696.75) by the end of 2nd dose increment (from 2097.32 to 2076.11) .It has also been found that as number of blood transfusion increasesalong with the child's age, we need to increase dose of deferasirox to control iron overload. By the time of 2$^{nd}$ increment in dose, around mean of (42.12 ) blood transfusions have been received and maximum per kg dose of deferasirox (40mg\kg\day)is reached. Beyond this Deferasirox alone fails in controlling further rise in ferritin levels, necessitating dual therapy by introducing 2$^{nd}$ iron chelator(either deferoxamine, deferiprone or some new iron chelator), also prevention and treatment of infections, parental counselling stressing on importance of timely blood transfusion and compliance fordrug intake in these patients are other measures that will ultimately help in decreasing iron overload and progression of associated organ damage.

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