



A study on safety and efficacy of Deferasirox, an oral iron chelator in the treatment of transfusion haemosiderosis in children with β -Thalassemia Major in a tertiary care rural hospital

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Abstract

Background: *β -Thalassemia major is a hereditary hemolytic anaemia (and the commonest transfusion dependent anaemia) which continues to be a major cause of morbidity and mortality in developing countries like India. Deferasirox is a tridentate, once-daily, oral iron chelator that is widely used in the management of patients with transfusion haemosiderosis. Chelation therapy is usually started after 10-20 transfusions or when serum ferritin level reaches 1000 $\mu\text{g/L}$ [Deferasirox has demonstrated consistent dose-dependent efficacy, producing sustained reductions in serum ferritin 6].*

Aims and objective

Aim: *To study the safety and efficacy of Deferasirox in transfusion haemosiderosis in children with β -Thalassemia.*

Objectives *1. To assess the serum ferritin levels in multi-transfused β -Thalassemia patients who are on treatment with Deferasirox. 2. To study the efficacy of Deferasirox in patients admitted with transfusion haemosiderosis in β -Thalassemia. 3. To estimate iron overload in the patients admitted with transfusion haemosiderosis in β -Thalassemia. 4. To study the adverse effect profile and final outcome of administration of Deferasirox in patients with transfusion haemosiderosis in β -Thalassemia.*

Study Period: *6 months (After the approval from IEC- RMC)*

Sample Size: *100* **Results and Observation** *there was a decrease in serum ferritin from 4049.87ng/ml to 3647.4ng/ml this was a significant change with a p value of 0.0001. Furthermore, a significant negative correlation was observed between the mean dose of deferiasirox prescribed and the mean serum ferritin levels. (%). Diarrhoea was reported as the most common) in our study it was found that the mean change in the serum creatinine values increased from 0.475 to 0.487 (table 7) in our study this change was not significant (table 6) the findings for sodium and serum potassium were not considered significant (table 7 and 8) in our study. awareness among prescribers about ADRs of deferiasirox and frequent monitoring of serum ferritin and serum iron levels as a guide to determine its dose is required to improve tolerability of this important and necessary drug. further multi-centered studies with more sample size are needed.*

Introduction

β -Thalassemia major is a hereditary hemolytic anaemia (and the commonest transfusion

dependent anaemia) which continues to be a major cause of morbidity and mortality in developing countries like India. Studies have shown that the

overall prevalence of β -thalassemia in India is 3-4% with an estimate of around 8,000 to 10,000 new births with major disease each year^[1]. An excessive number of blood transfusions has improved the life expectancy of thalassemia major patients over the decades but iron overload is an unavoidable complication resulting from multiple blood transfusions, ineffective erythropoiesis and increased gastrointestinal iron absorption which can lead to organ damage and increased mortality^[2,3]. The frequency of its occurrence has led to its reference as a 'second disease' during treatment of β -Thalassemia^[4] and may result in organ dysfunction of liver, heart, pituitary or pancreas which can be fatal. Cardiac haemosiderosis is the most life threatening complication of iron overload and a major cause of mortality. In these children, iron deposition in parenchymal tissues begins within 1 year of starting the regular transfusions^[5]. Iron overload impairs the immune system, placing them at greater risk of infection and illness. **Deferasirox** is a tridentate, once-daily, oral iron chelator that is widely used in the management of patients with transfusion haemosiderosis. Chelation therapy is usually started after 10-20 transfusions or when serum ferritin level reaches 1000 $\mu\text{g/L}$ ^[6]. In the absence of physiological mechanisms to excrete this excess iron resulting from transfusions, administration of effective iron-chelation therapy is the only way to prevent end-organ damage. Only few studies were carried out on the efficacy and safety evaluation of Deferasirox in India or around the world. Chronic iron overload represents a serious complication of potentially life-saving regular blood transfusions which are administered for a variety of congenital and acquired types of anaemia. Iron from frequent blood transfusions deposits mainly in the liver, endocrine organs, and heart.^[7,8] Patients with chronic anaemia such as thalassemia, sickle cell disease, congenital rare anaemia and myelodysplastic syndromes require regular blood transfusions in order to improve both Quality of Life (QOL) and survival. Human body is unable

to eliminate the iron released from the breakdown of transfused red blood cells and the excess iron is deposited as hemosiderin and ferritin in the liver, spleen, endocrine organs and myocardium.^[9] The accumulation of toxic quantities of iron causes tissue damage and leads to complications such as heart failure, diabetes, hypothyroidism, liver failure and early death.^[9,10] Morbidity and mortality in regularly-transfused thalassemia patients are primarily due to the effects of iron overload rather than to the underlying disease, with over half of all deaths attributable to cardiac complications.^[9] Packed Red Blood Cells (PRBC) contain approximately 1 mg of elemental iron per ml. Evidence of iron overload is generally apparent after about 100 to 120 ml/kg of PRBC have been administered which is equivalent to 20 to 30 adult units.^[11-13] In frequently transfused thalassemia patients, the total body iron burden is estimated to increase at a rate of 2 to 5 grams of iron per year.^[11] The accumulation of iron in the body is reflected by a measurable increase in serum ferritin levels. Increased morbidity and mortality are observed in patients with serum ferritin values above 2500 ng/ml.^[10] In the absence of chelation therapy, iron overload leads to the development of multi-system organ dysfunction, ultimately concluding in death in all patients.^[14] Without chelation therapy, patients generally develop cirrhosis between the ages of 10 to 15 years, but mild cirrhosis has been observed as early as 8 or 9 years of age.^[15] Endocrine complications including pituitary and gonadal failure are common even early in life leading to growth failure and delayed development of secondary sexual characteristics. The development of diabetes mellitus by early in the second decade of life is frequent. Cardiac complications, often manifest as congestive heart failure, have a peak incidence between the ages 10 to 15 years.^[11,16] Consequently, regularly transfused patients with β -thalassemia major who do not receive or who do not comply with chelation therapy to remove excess iron do not survive past the third decade of life due to the cumulative toxic effects of iron

resulting in organ failure. A variety of epidemiological data are consistent and indicates that in the absence of good compliance with an adequate regimen of chelation therapy, cardiomyopathy attributable to iron overload is the most frequent cause of death in patients with β -thalassemia major.^[11,17] Diseases such as β -thalassemia, once fatal in early childhood, can now be managed as chronic conditions compatible with prolonged life with life expectancy varying between 25 and 55 years, depending on patients' compliance with medical treatment, particularly iron chelation therapy.^[18] The efficacy and safety profiles of Deferasirox have been studied in a series of 1-year Phase II and III registration studies involving more than 1,000 patients, including 433 patients aged between 2 to 15 years. These studies led to Food and Drug Administration (FDA) approval of Deferasirox with an orphan drug designation. In clinical trials, Deferasirox has demonstrated consistent dose-dependent efficacy, producing sustained reductions in serum ferritin, labile plasma iron, and cardiac iron load. Some of the Phase II and III registration studies conducted on Deferasirox described a defined, clinically manageable safety profile across all age groups, including patients as young as 2 years of age. Across the core trials, the most common drug-related adverse events were gastro-intestinal disturbances and rashes.^[19-21] Non-progressive increases in serum creatinine were observed in approximately one-third of patients treated with Deferasirox.^[20] These increases were dose dependent, often resolved spontaneously and could sometimes be alleviated by reducing the dose.^[21]

This study will focus on the safety and efficacy of Deferasirox in transfusion haemosiderosis in children with β -Thalassemia in a rural setting.

Aims and Objectives

Aim

To study the safety and efficacy of Deferasirox in transfusion haemosiderosis in children with β -Thalassemia.

Objectives

- 1) To assess the serum ferritin levels in multi-transfused β -Thalassemia patients who are on treatment with Deferasirox.
- 2) To study the efficacy of Deferasirox in patients admitted with transfusion haemosiderosis in β -Thalassemia.
- 3) To estimate iron overload in the patients admitted with transfusion haemosiderosis in β -Thalassemia.
- 4) To study the adverse effect profile and final outcome of administration of Deferasirox in patients with transfusion haemosiderosis in β -Thalassemia.

Material and Methods

This is an observational study, which will include β -Thalassemia pediatric patients registered in Medical College from April, 2017 to September, 2017.

Type of study- It will be a prospective longitudinal study.

Study setting- Pediatric Ward of Medical College.

Study population- Pediatric patients admitted for β -thalassemia from study period April, 2017 to September, 2017. Prospective study began after Institutional Ethics Clearance (IEC) approval.

Enrolled patients were subjected to the following inclusion and exclusion criteria;

1) Inclusion criteria

All patients with β -Thalassemia showing transfusion haemosiderosis and treated with Deferasirox.

All patients with β -Thalassemia showing transfusion haemosiderosis falling under the pediatric age group.

All patients with β -Thalassemia showing transfusion haemosiderosis belonging to either gender.

All patients with β -Thalassemia showing transfusion haemosiderosis ready to give written and informed consent.

All patients with β -Thalassemia showing transfusion haemosiderosis willing to remain in the location of study (Medical College) till discharge.

2) Exclusion criteria

Patients with β -Thalassemia showing transfusion haemosiderosis not administered Deferasirox as a chelation drug.

Patients with transfusion haemosiderosis due to other etiological factors like, Aplastic anaemia, Sickle cell disease, Myelodysplastic syndrome, Hemolytic anaemia and refractory sideroblastic anaemia.

Patients with β -Thalassemia showing transfusion haemosiderosis are not willing to give a written and informed consent for inclusion in the study.

Patients with β -Thalassemia showing transfusion haemosiderosis not willing to remain or be

hospitalized for complete duration of the research in the location of study (Medical College).

Study period- 6 months (After the approval from IEC- RMC)

Sample size-100

Data analysis-All the data related to above variables was pulled from the case record forms and tabulated in an excel sheet. Observation tables were prepared according to the objectives to be satisfied and subjected to statistical tests.

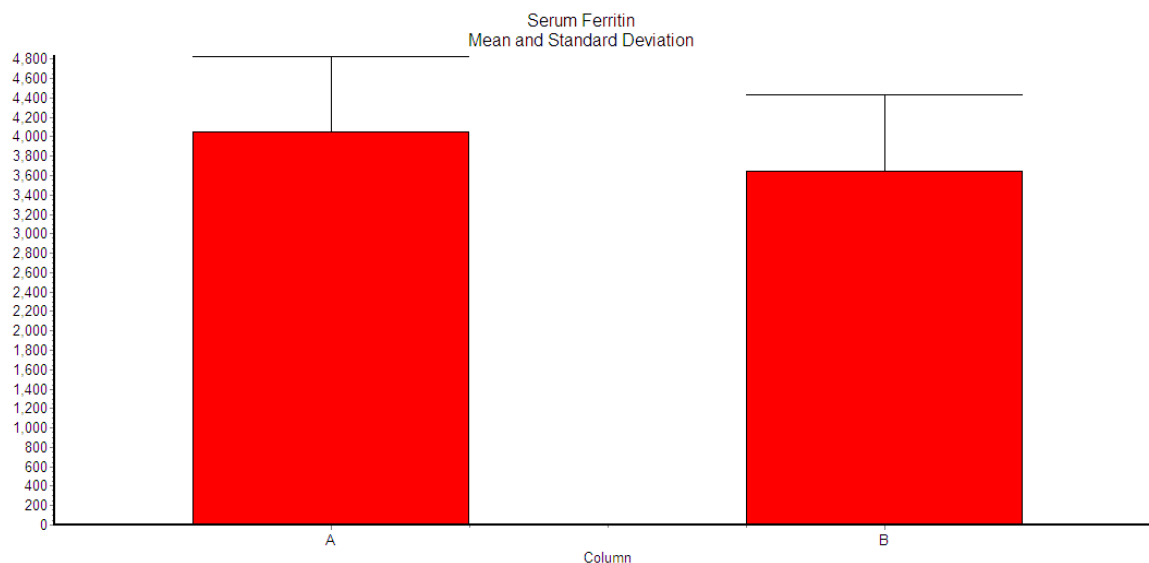
Statistical analysis- Descriptive statistics was used, percentage mean, median and mode, inferential statistics, test of significance were applied to appropriate observations to draw inferences

Observation and Results

Table 1: Serum Ferritin

	Value at initiation of the study	Value at end of the study
Average	4049.879167	3647.40833
Standard Deviation	776.1780807	782.964688

Graphical representation of Table 1

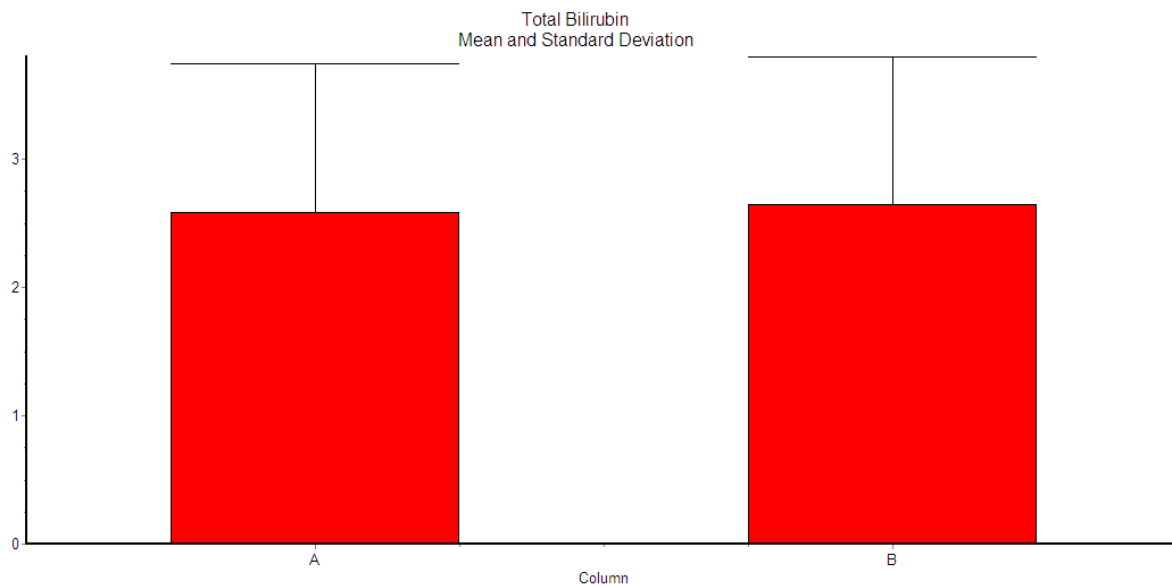


The two-tailed P value is < 0.0001, considered extremely significant.
 t = 20.288 with 23 degrees of freedom

Table 2: Total Bilirubin

	Value at initiation of the study	Value at end of the study
Average	2.59166667	2.64583333
Standard Deviation	1.15642503	1.1560725

Graphical representation of Table 2

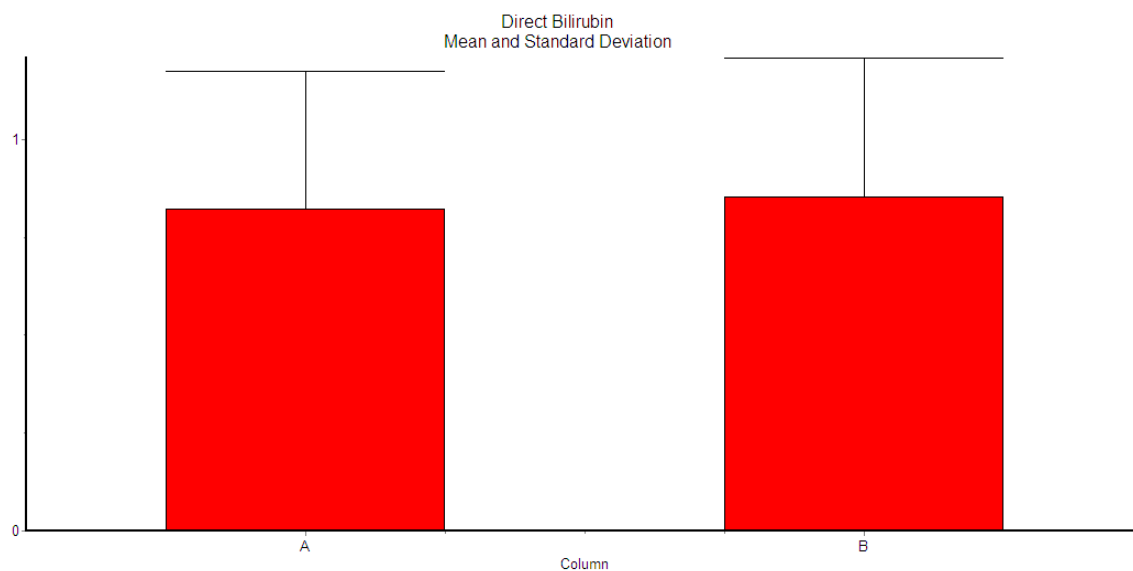


The two-tailed P value is 0.0137, considered significant.

Table 3: Direct Bilirubin

	Value at initiation of the study	
Average	0.8208333	0.85416667
Standard Deviation	0.3538351	0.3538351

Graphical representation of Table 3

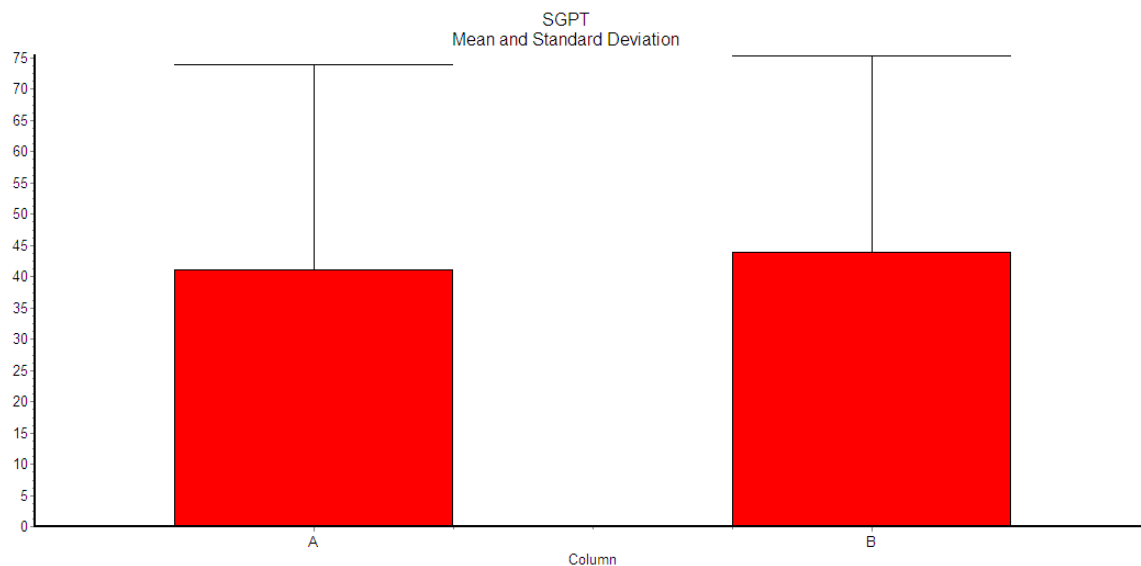


The two-tailed P value is 0.0024, considered very significant.

Table 4: SGPT/ALT

	Value at initiation of the study	
Average	41.125	43.875
Standard Deviation	32.70728213	31.40383873

Graphical representation of Table 4

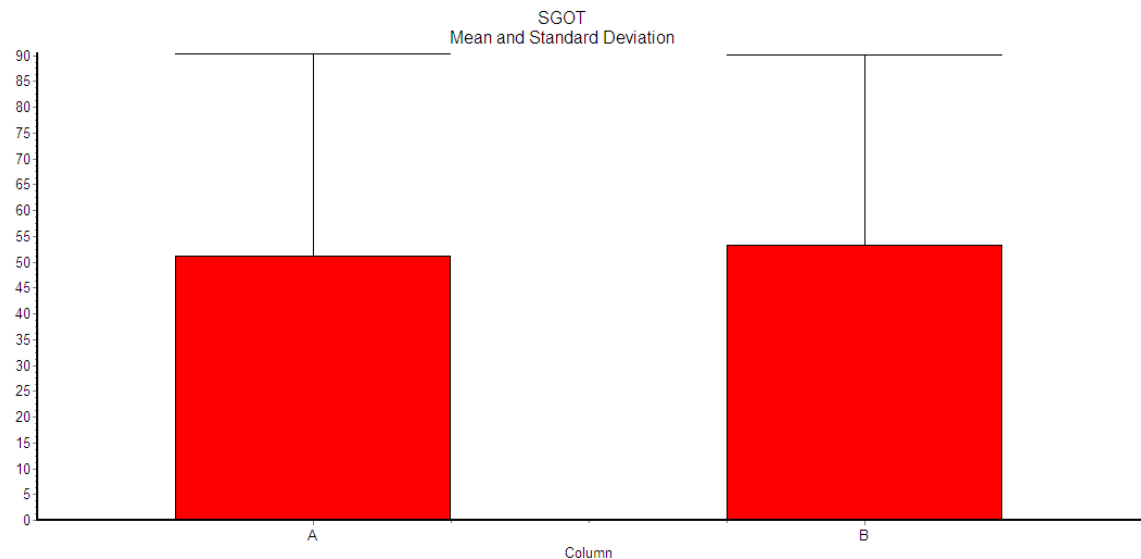


The two-tailed P value is 0.0005, considered extremely significant.

Table 5: SGOT/AST

	Value at initiation of the study	
Average	51.25	53.33333333
Standard Deviation	39.09659165	36.87306861

Graphical representation of Table 5

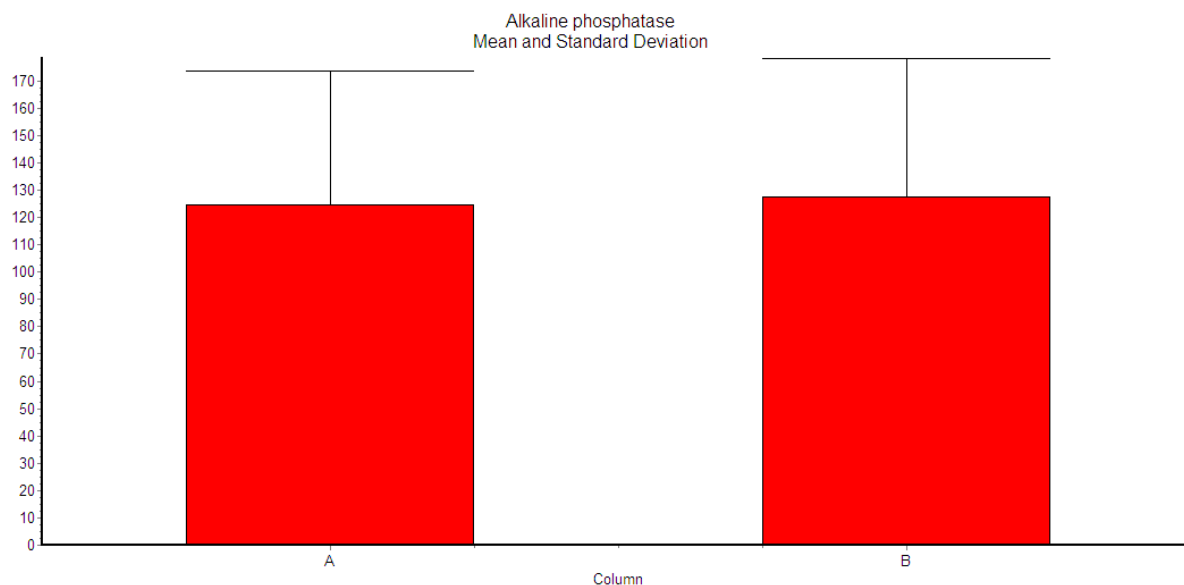


The two-tailed P value is 0.0034, considered very significant.

Table 6: Alkaline phosphatase

	Value at initiation of the study	
Average	124.7916667	127.5416667
Standard Deviation	48.9844511	50.65739928

Graphical representation of Table 6

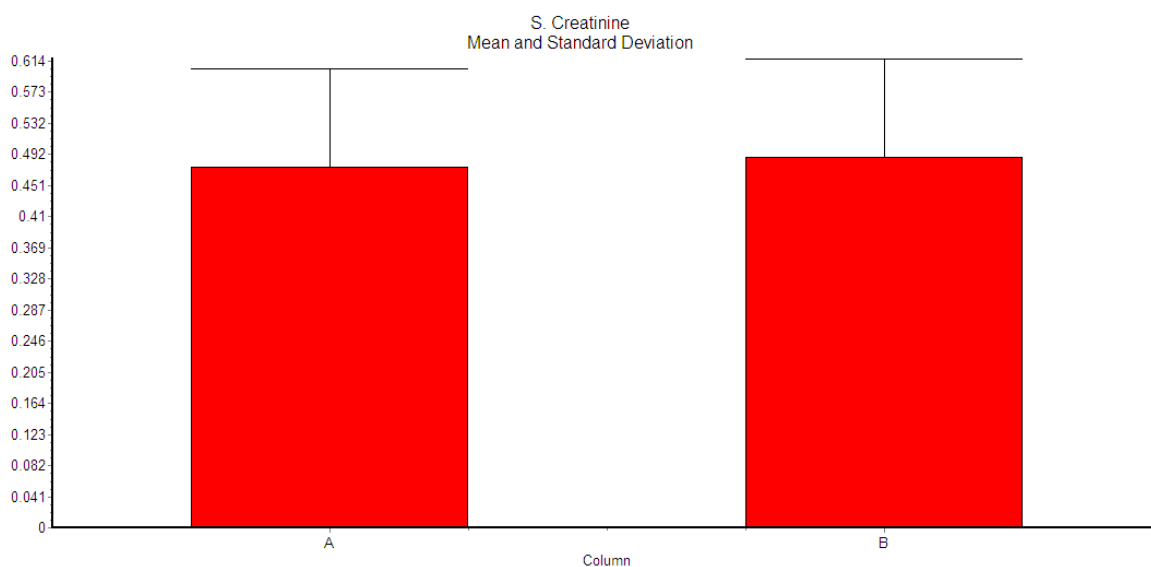


The two-tailed P value is 0.0125, considered significant.
 t = 2.710 with 23 degrees of freedom.

Table 7: Serum Creatinine

	Value at initiation of the study	
Average	0.475	0.4875
Standard Deviation	0.129379791	0.129589653

Graphical representation of Table 7

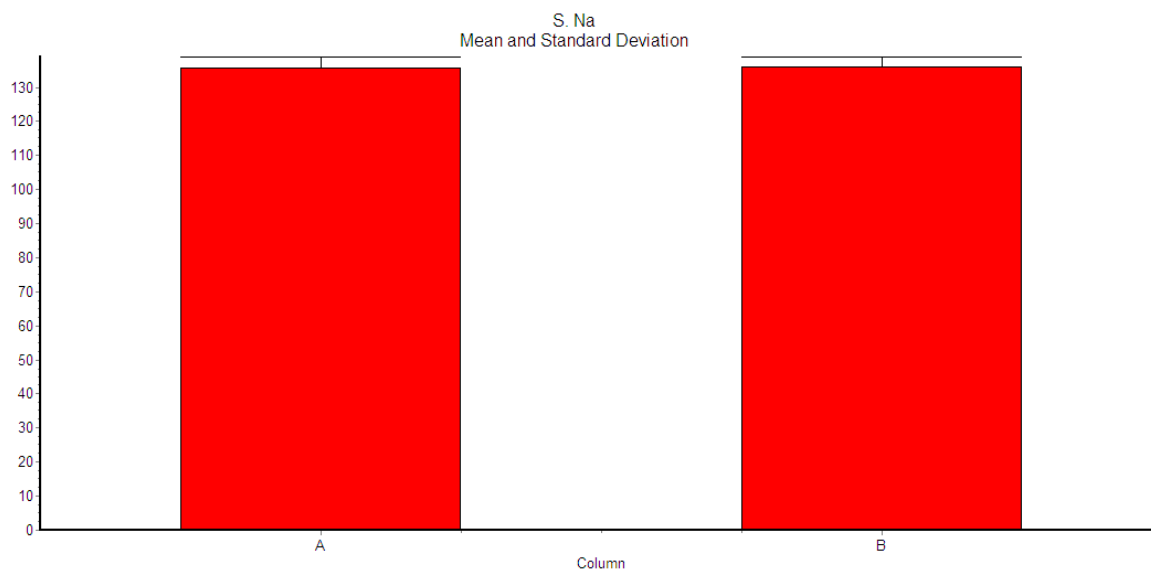


The two-tailed P value is > 0.9999, considered not significant.

Table 8: Serum Sodium

	Value at initiation of the study	
Average	135.5625	135.875
Standard Deviation	3.36824203	3.02615411

Graphical representation of Table 9

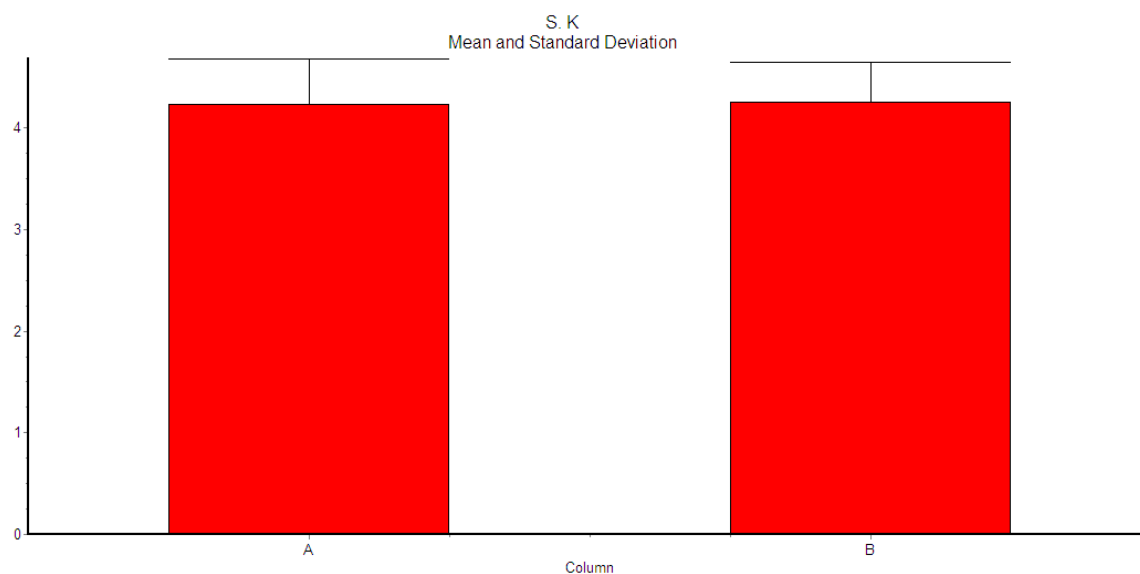


The two-tailed P value is 0.0760, considered not quite significant.

Table 9: Serum Potassium

	Value at initiation of the study	
Average	4.23333333	4.2541667
Standard Deviation	0.44786126	0.3977974

Graphical representation of Table 10



The two-tailed P value is 0.2329, considered not significant

Discussion

Thalassemia, a heterogeneous group of inherited disorders of haemoglobin synthesis, is the world's most common monogenic diseases. An estimated 80–90 million people in the world carry the beta thalassemia trait. The disease is also common in

India with approximately 10,000–12,000 children born every year with β thalassemia major.^[1] India contributes to approximately 10% of the global disease burden.² Defective production of β globin chains in β thalassemia leads to an increased production of α globin chains. These globin chains

get precipitated in RBCs, leading to extensive haemolysis and anaemia. Resultant hypoxia and increased erythropoietin production cause expansion of ineffective erythroid mass. Definitive treatment of thalassemia includes bone marrow transplantation and gene therapy, both of which are expensive. In resource-limited settings, repeated BTs remain the mainstay of management. However, repeated BTs lead to iron overload and deposition of iron in various tissues of the body.^[6] Iron overload is associated with a variety of complications affecting skeletal, cardiovascular, hepatobiliary, and endocrine systems. Hepatotoxicity due to iron overload is one of the leading causes of death in patients suffering from thalassemia.^[7,10,11] To prevent these complications, iron chelation therapy is now recommended and routinely prescribed to transfusion dependent thalassaemic patients.^[12] Conventional iron chelators, i.e., desferioxamine and deferiprone, are effective in reducing iron overload. However, these drugs, owing to a shorter half-life, require frequent administration. In the present study we used deferacerox as an iron chelating agent in a dose of 20 to 30mg/kg body wt, for mean serum ferritin and mean serum iron levels were observed in all groups (table 1) there was a decrease in serum ferritin from 4049.87ng/ml to 3647.4ng/ml this was a significant change with a p value of 0.0001. Furthermore, a significant negative correlation was observed between the mean dose of deferasirox prescribed and the mean serum ferritin levels. These findings suggest that deferasirox effectively reduced iron overload. A phase III study also showed a significant decrease in serum ferritin levels (mean reduction of $1137 \pm \text{ng/ml}$ ⁴⁵³) with deferasirox treatment (30mg/kg/day) in 296 transfusion-dependent β thalassemia patients over a period of 1 year^[22]. In the same study, serum ferritin levels were stabilized at 20 mg/kg/day of deferasirox Pennell *et al.*^[23]. Also reported a median reduction of 1048 ng/ml in serum ferritin from baseline over 1 year in transfusion dependent.

In the present study, all patients received deferasirox in doses ranging from 20 to 30 mg/kg/day. While adherence to drug administration guidelines^[4] was observed in majority of the patients, concomitant use of food and improper dispersion of deferasirox was observed in 27.3% patients. This can be avoided by education of patients and caretakers regarding proper administration of deferasirox. In the present study, the mean number of BTs received was higher in age groups of more than 3 years baseline as compared to children aged 1–3 years. A significantly higher mean dose of deferasirox was prescribed to patients in higher age groups at baseline as compared to those aged 1–3 years. Furthermore, in each age group, the mean dose of deferasirox prescribed at the end of study period was significantly higher as compared to that at the baseline. The number of BT increases with age of the patient. This also increases iron overload proportionately. Hence, the requirement of a higher dose of deferasirox in these age groups was justified. An increment in dose of deferasirox was employed in patients of 1–3 years and 4–6 years to reduce iron overload and achieve target serum ferritin levels. High-serum ferritin levels require dose increment in older children; however, this was not observed in the present study. ADRs were observed in nearly 95% patients. Higher incidence of ADRs in these patients can be attributed to the prolonged and continuous use of deferasirox. A positive correlation between the dose of deferasirox prescribed and the number of ADRs observed per dose was present. Taher *et al.*⁽²⁴⁾ have also reported a higher incidence of ADRs in patients receiving 30 mg/kg/day deferasirox as compared to those receiving a daily dose of 20 mg/kg. Most common ADR in the present study was diarrhea with or without blood (22.2%). Diarrhoea was reported as the most common in our study it was found that the mean change in the serum creatinine values increased from 0.475 to 0.487 (table 7) in our study this change was not significant (table 6) the findings for sodium and serum potassium were not considered significant

(table 7 and 8) in our study. In our study the change in serum creatinine was not significant it might be due to low sample size. The present study, which included raised serum creatinine, raised transaminase, diarrhea with or without blood, and jaundice. These ADRs recovered with supportive treatment and temporary withdrawal of the drug for a mean duration of 18 ± 8.2 days. Cappellin *et al* had also reported diarrhea, raised serum creatinine, and raised serum transaminase as the most common dose-dependent ADRs with deferasirox which require temporary withdrawal of drug. Majority (94.1%) of ADRs observed were definitely preventable. These observations suggest that deferasirox was well tolerated and relatively safe in transfusion-dependent pediatric patients of thalassemia. Majority of the ADRs were reported with higher doses of deferasirox, suggesting the need for routine monitoring of serum ferritin and maintaining the patients on lowest effective dose possible. An awareness among prescribers about ADRs of deferasirox and frequent monitoring of serum ferritin and serum iron levels as a guide to determine its dose is required to improve tolerability of this important and necessary drug.

Conclusion

Deferasirox is relatively well tolerated among these patients. Deferasirox is least tolerated in the dose of 30 mg/kg/day. Periodic monitoring of laboratory and clinical parameters along with suitable dose modification can help optimize the drug therapy and improve the safety of this drug. Caution should be exercised for the right method of drug administration to improve efficacy and minimize ADRs due to deferasirox. Majority of the ADRs were reported with higher doses of deferasirox, suggesting the need for routine monitoring of serum ferritin and maintaining the patients on lowest effective dose possible. An awareness among prescribers about ADRs of deferasirox and frequent monitoring of serum ferritin and serum iron levels as a guide to determine its dose is required to improve tolerability of this important and necessary drug.

further multi-centered studies with more sample size are needed.

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