

## Original Research Article

# Ocular manifestations in multitransfused thalassemic children on chelation therapy

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## ABSTRACT

**Background:** Beta-thalassemia is the most common form of thalassemias. It is due to mutations involving the beta globin gene. The objective of this study was to study ocular manifestations in multi transfused thalassemic children and to assess the possible ocular side-effects with deferasirox.

**Methods:** This was a prospective correlational study. After obtaining institutional ethical committee clearance, children with beta-thalassemia who came for regular blood transfusions were assigned into group A and group B based on whether they received deferasirox therapy or not. They were sent for detailed ophthalmological examination. The details about number of blood transfusions, serum ferritin and chelation therapy was obtained from the treatment records. The ocular manifestations were documented and later correlated to the blood transfusions, Serum ferritin levels and the chelation therapy.

**Results:** Out of 50 children, 42 children belonged to group A and 8 belonged to group B. The male to female ratio was 2.2:1 in group A and 1:3 in group B respectively. The number of blood transfusions received was 67.7 versus 21.87 in group A and B respectively. The mean frequency of blood transfusions was 5.26 weeks vs 3.8 weeks in group A and group B respectively. Mean serum ferritin was higher in group A (912.19 mcg/l) compared to 665 mcg/l in group B. Out of 50 children 7 had ocular findings (p value: 0.176), statistically not significant. All of them belonged to group A. Only 3 of them had lenticular opacities and 4 of them had refractory errors. The mean serum ferritin and the number of blood transfusions received were higher in children with ocular findings than in those with no ocular manifestations. Serum ferritin in those with lenticular opacities was 1363.66 mcg/l and in those with refractory error was 987.25mcg/l. The average blood transfusion received was 104.6 in those with lenticular opacities and 62.25 in those with refractory errors.

**Conclusions:** Regular ocular examinations can aid in preventing, delaying or reducing the ocular complications in transfusion dependent beta-thalassemia major children.

**Keywords:** Deferasirox, Thalassemia, Iron overload, Ocular manifestations

## INTRODUCTION

Beta-thalassemia is the most common form of thalassemias. It is due to mutations involving the beta globin gene. There is disruption in red blood cell maturation leading to ineffective erythropoiesis.<sup>1</sup> Repeated blood transfusions are required in beta-

thalassemia major which inevitably leads to iron overload.<sup>1</sup> Iron accumulates in many tissues like heart, liver, skin, eyes etc. leading to multi organ damage. To reduce these systemic complications of siderosis, iron chelating agents are being used. But these agents not only chelate iron but also copper, zinc, cobalt and nickel which are essential for normal retinal function.<sup>1</sup> Ocular

changes like cataract, optic neuropathy, retinal pigment epithelial (RPE) degeneration, retinal venous tortuosity, vitreoretinal hemorrhages are documented in children with beta- thalassemia.<sup>1-3</sup> These manifestations can be secondary to iron or iron chelating agents.<sup>1</sup> Desferrioxamine, deferiprone, deferasirox are the common iron chelating agents that are used.<sup>4</sup> Ocular side effects have been reported with the former two, but there are not many studies associating Deferasirox and ocular toxicity.<sup>4</sup>

The aim of the present study was to find the ocular manifestations in multi transfused thalassemic children and assess the possible ocular side-effects of deferasirox, the most commonly used chelating agent in our hospital.

## METHODS

A cross-sectional study conducted in the rural field. This was a prospective cross-sectional study conducted in the Department of Pediatrics, Cheluvamba Hospital, Mysore. Study period was for a period of 12 months from June 2016 to June 2017. Considering a prevalence of 3/100 in our hospital, a sample size of 50 was obtained.

### Inclusion criteria

Children with  $\beta$  thalassemia major on regular transfusions with or without Deferasirox therapy were included.

### Exclusion criteria

- Hemoglobinopathies other than  $\beta$  thalassemia major
- Children suffering from congenital and acquired ocular anomalies not related to blood transfusion.

After entering the demographic details, these children were sent for a detailed ophthalmological examination. Visual acuity, visual field, slit lamp examination, fundoscopy and color vision testing was done on both the eyes by an ophthalmologist and the findings were documented. The details about transfusion, serum ferritin levels and chelation therapy were entered into the proforma following the ophthalmological evaluation. The information regarding this was obtained from the hospital discharge records. The enrolled children were divided into two groups based on the chelation therapy.

Group A consisted of those children who received only blood transfusion and Group B consisted those who received both blood transfusion and deferasirox. The relationship between the number of transfusions, ocular changes and chelation therapy was analysed subsequently. p value less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software. Correlation of ocular findings with serum ferritin levels, average number of blood transfusions received, deferasirox therapy was done by Pearson's correlational analysis with two-tailed p value <0.05 taken as significant.

## RESULTS

Table 1 shows the baseline characteristics of the study group. Of the 50 enrolled patients, 42 (84%) received both blood transfusion and deferasirox therapy and were assigned group A. The remaining 8 (16%) received only blood transfusion and were assigned group B. The mean age in group A and B was 8.8 years and 4 years respectively. Of the 42 in group A, 29 were male and 13 were female. In group B, 2 were male and 6 were female. 22 (44%) patients were diagnosed to be suffering from beta-thalassemia within the first year of life, of whom 15 (68%) were diagnosed within six months of life. 17 (34%) patients were diagnosed between the ages of one and two years, 6 (12%) between two and three years and 5 (10%) after the age of three. The mean age at diagnosis was 1.39 years and 2.18 years in group A and B respectively.

**Table 1: Baseline characteristics of the study group.**

Characteristics	Group A (n=42)	Group B (n=8)	P value
Age (years)	8.88	4	<0.05
Male/female	29/13	2/6	0.33
Weight (kg)	20.64	12.12	<0.05
Age at diagnosis (years)	1.39	2.18	0.108
No. of BT received	67.71	21.87	<0.05
annual BT (ml/kg/year)	102.71	119	0.476
Annual transfusion Fe load (mg/kg)	0.18	0.21	0.472
Freq of BT in weeks	5.26	3.81	<0.05
Pre-transfusion Hb	7.81	7.98	0.594
Sr ferritin	912.19	665	<0.05

All values as mean (SD) unless specified; BT: Blood transfusion; Fe: Iron; Hb: hemoglobin.

The average number of transfusions received was 67.7 (range: 29 to 132) in Group A and 21.87 (Range:12 to 60) in Group B. The annual blood transfusion (ml/kg/year) was 102.7 in group A and 119 in group B. While the annual iron load is 0.18 in group A and 0.21 in group B. The frequency of blood transfusion was 5.2 weeks (range: 3.2 to 10) in group A and 3.8 weeks (range: 3 to 4) in group B. Pre-transfusion Hb was 7.8 g% (range: 6.2 to 9.8) and 7.98 g% (range: 6.4 to 9.4) in group A and B respectively. The serum ferritin levels were 912 mcg/L (range: 556 to 1840) and 665 mcg/L (range: 540 to 854) respectively in group A and B. The mean dose of deferasirox was 25.63±5.692g. The average duration of deferasirox was 4.88±3.038 years, the range being 1-14 years.

Table 2 shows ocular involvement in different groups of thalassemic patients. Overall, 7 (14%) patients had some ocular involvement, p value: 0.176, statistically not significant. 43 (86%) subjects had normal visual acuity.

**Table 2: Ocular manifestations in the study group.**

Opthal findings	Group A	Group B	Total
Lenticular opacities	3 (7.1%)	0	3 (6%)
Refractory errors	4 (9.5%)	0	4 (8%)
None	35 (83.3%)	8	43 (86%)
Total	42 (100%)	8 (100%)	50 (100%)

**Table 3: Relationship between ocular findings, serum ferritin and number of blood transfusions.**

Ocular findings	Serum ferritin	No. of blood transfusions
None	827.72	57.116
Lenticular opacities	1363.6	104.66
Refractory errors	987.25	62.25

In all subjects, near visual acuity was normal. Lenticular opacities seen in thalassemic patients mainly comprised posterior sub capsular haze and posterior cortical opacities. None of these opacities were in the visual axis and therefore none interfered with the vision. Overall, 3 (71%) patients had lenticular opacities and all of them belonged to group A.

None of the patients showed any abnormality on visual field testing. In those with decreased visual acuity, refractive error was found to be the cause. Overall 4 (9.5%) in group A and none in group B had near vision. The refractory error was fully correctable with glasses. Thus, of the 8 patients who received only deferasirox therapy, no one had any ocular manifestations.

In those without ocular manifestations, the average serum ferritin levels and average number of blood transfusions received was 827.7mcg/L and 57.16 respectively while in those with lenticular opacities, it was 1363.66 mcg/L and 104.66 respectively. In those with refractory errors, the average serum ferritin was 987.25 mcg/L and the average number of Blood transfusions received was 62.25 (Table 3).

## DISCUSSION

Patients suffering from thalassemia present with varied ocular and systemic manifestations. Ocular findings is said to range from decreased visual acuity, color vision anomalies, night blindness, cataract, visual field defects and optic neuropathy. Iron-chelating agents like desferrioxamine and deferiprone are reported to cause many of these ocular changes. Studies of ocular changes in thalassemics using deferasirox are very few. In the present study, we studied the various ocular manifestations of multi transfused thalassemics with and without deferasirox chelation.

In the present study, patients belonged to the age group 18 months to 17 years. However, similar studies in the

Western world have also been performed in patients of up to 45 years of age. This age disparity can be attributed to lower survival rates among thalassemics in the Indian subcontinent, unlike the West.<sup>1</sup> Reasons for this seem to be poor compliance with therapy, difficulty in obtaining regular blood transfusions and high cost of iron chelation therapy.<sup>1</sup> The literature provides no clue as to whether thalassemia is more preponderant in a particular sex.<sup>1</sup> In the present study, a slight male preponderance (1.6:1) was observed over females. This is consistent with the studies of Gartaganis et al and Gaba et al where ratios of 1.07:1 and 1.33:1 respectively, were observed.<sup>3,5</sup>

Frequency of ocular involvement in the present study was 14%. Gartaganis et al reported figures of 41.3% while Gaba et al reported ocular involvement in 71.4% of subjects in their respective studies. Our figure of 14% is significantly less compared to these above studies. Age at diagnosis was directly related to the time at which anemia manifests itself. In the present study, only 22/50(44%) of patients were diagnosed within the first year of life. In the study conducted by Gaba et al, 55% patients were diagnosed in the first year of life.<sup>5</sup> An early diagnosis needs to be done so that blood transfusion can begin early and the treatment option of bone marrow transplantation can be given at the earliest. Blood transfusions in beta-thalassemia major aims to maintain a level of hemoglobin at 10-14 g/dl (post transfusion). The average number of blood transfusions in the present study was 44.7. In the study by Gaba et al study, the average number of transfusions received was 142. This can be explained due to average transfusion interval of 5.26 weeks in Group A children who formed the majority.

3 out of 50 subjects (7%) in the present study had lenticular opacities. Gartaganis et al and Gaba et al, in their respective studies, found lens opacities in 13.8% and 45.7% of subjects. None of these opacities were in the visual axis and none therefore interfered with vision. In the present study, lens opacities correlated significantly with higher serum ferritin levels and number of blood transfusions received ( $P < 0.05$ ). This is consistent with the findings of Gaba et al.<sup>5</sup> Iron-chelating agents too have been implicated in the causation of lens opacities. Gartaganis et al, in their study found no correlation between occurrence of lens opacities and dose of desferrioxamine received.<sup>3</sup> The opposite was found in Gaba's et al study. The present study results are consistent with those of Gartaganis et al ( $P < 0.05$ ) as there are no lenticular opacities in those receiving deferasirox. This could possibly be due to adequate chelation or could be due to the fact that children in group B are of younger age group and have received relatively lesser transfusion, hence lesser iron overload and near normal serum ferritin levels.

In the present study, unaided visual acuity was found normal in 43 (86%) patients while in Gaba et al study, the figure was 62.9%. Recent studies conducted by Taher et al in 2006 have found normal visual acuity in 80.6%

subjects.<sup>6</sup> Taher et al. also found that the type of iron-chelating agent used had no influence on decrease in the visual acuity.

Taher et al reported retinal pigment epithelial degeneration, retinal degenerations and retinal venous tortuosity.<sup>6</sup> Similar observations were reported by Gaba et al. However, none of these retinal changes were demonstrated in the present study.

## CONCLUSION

A long follow-up is required to analyse and comment on how ocular changes may evolve. The limitation of the present study is that it cannot conclusively establish whether ocular changes are a result of the disease per se or due to iron-chelating agents. It should be kept in mind that iron overload and iron-chelating agents both are mutually confounding factors in the causation of ocular changes of thalassemia.

A study on newly diagnosed cases of thalassemia who are not on any treatment as well as those on a long-term follow-up is needed in order to ascertain the development and evolution of ocular changes.

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