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Effects of deferoxamine versus deferasirox on hematology and liver parameters in children with beta-thalassemia major: A cross-sectional study from a single center

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Abstract

Background: Iron chelating agents (ICAs) may induce changes in the blood and the liver indices. This study aimed to compare the effects of deferasirox (oral) and deferoxamine (parenteral) on the hematological and liver indices.

Materials and Methods: A cross-sectional study was conducted on patients at the Thalassemia Center in Sulaymaniyah, Iraq. The study included 76 β-thalassemia major children (37 females and 39 males, with a median age of 6 years). The patients were divided into Group I (n = 51, treated with deferasirox) and Group II (n = 25, treated with deferoxamine). Complete blood count and liver enzymes (alanine [ALT] and aspartate [AST] aminotransferase) were determined; the hemoglobin densities were calculated to differentiate absolute from restrictive iron deficiency; and the fibrosis-4 score (FIB-4, aspartate-to-platelet ratio index (APRI), and (AST/ALT ratio) were calculated.

Results: Hemoglobin density indices showed restricted iron deficiency in both treated groups. However, serum ferritin level was higher in Group II than in Group I (1.9 times higher, p=0.037).

Also, the median value of MCV in Group II was significantly higher than in Group I (79.8 fL vs. 77.0 fL, respectively). In contrast, liver fibrosis indices defined with the mean values of AST-to-ALT ratio and FIB-4 score were higher in Group I compared to Group II. A positive and significant correlation was observed between APRI level and serum ferritin in Group I ($r = 0.518$, $df = 49$, $p<0.001$).

Conclusions: Based on the data, it can be concluded that both deferasirox and deferoxamine affect red blood cells parameters, which may be related to their function as ICAs, leaing to temporary iron deficiency in treated patients. Both drugs may induce inconsistent changes in the liver which are highly associated with circulating ferritin level. However, the destructive effect of deferasirox on the liver is more evident, leading to the induction of fibrosis

Keywords: β-thalassemia, Deferasirox, Deferoxamine, Liver fibrosis indices

Introduction

Beta-thalassemia was initially described by Cooley and Lee in 1925 (1), which is characterized by the absence or reduction in the production of the globin chain (2). It is usually managed by regular blood or blood product transfusions, which lead to iron overload in various organs. Therefore, iron chelating agents (ICAs) are used to overcome the iron overload and prevent its late sequel e.g., diabetes mellitus, hypopituitarism, hypothyroidism, liver cirrhosis, cardiomyopathy, etc. (3, 4).

Iron chelating agents, including deferoxamine (i.v. infusion), deferasirox (oral), and deferiprone (oral), are used to overcome the iron overload that occurs with regular blood transfusions (5). Higher levels of ferritin in biological fluids and organs are predictors of organ iron overload, irrespective of ICAs (6). Reduction of the serum ferritin, and hepatic iron overload will improve the outcome of patients with beta-thalassemia (7). A meta-analysis that included 1520 patients did not show specific ICAs that

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overcome organ iron overload, and there were no significant differences between ICAs in reducing ferritin levels (8). Previous studies did not demonstrate the effects of ICAs on the hematological indices (included red blood cell count, mean corpuscular volume [MCV], mean corpuscular haemoglobin [MCH], mean corpuscular haemoglobin concentration [MCHC], and red distribution width) that were used to differentiate β-thalassemia triat from iron deficiency anemia (9, 10). Moreover, the effects of these agents on the indices that indicate the existence of liver damage in terms of fibrosis and fatty infiltration (by calculating the fibrosis-4 score and the ratios of liver enzymes) were not carried out on children with β-thalassemia major (11). This cross-sectional study was aimed to highlight the changes in the laboratory hematological and liver indices in β-thalassemia patients managed with blood transfusions and deferoxamine or deferasirox.

Materials and Methods

Study design and participants

This cross-sectional study has been conducted on patients at the Sulaimani General Hospital, Thalassemia Center in Sulaymaniyah, Iraq from January 1 to May 31, 2023. The study protocol was approved by the Institutional Ethics & Research Registration Committee (No. PH 100-23; date: June 12, 2023). There is no need to obtain written consent from patients' parents or patients' proxy because the characteristics and laboratory data were obtained from the patient's record at the time of attending the center. Patients aged ≤ 12 years with β-thalassemia major (who were diagnosed by hemoglobin electrophoresis) were enrolled in this study. All of them received blood transfusions (either regularly or on demand) at varying intervals of 3 to 5 weeks. Blood transfusion was the cornerstone of the management of these patients, which was carried out every two weeks for patients who had haemoglobin (HB) levels of less than 9 g/dL. In addition, ICAs either deferoxamine or deferasirox, were used. Deferoxamine at a dose of 40 mg/kg, s.c. over a period of 12 hours each night for six days. Deferasirox at an oral dose of 30mg/kg/day was used to get a serum ferritin level of less than 1500μg/L. Deferasirox and deferoxamine were the only ICAs that available in the Thalassemia center, and most pediatricians preferred to prescribe deferasirox because this medication is safe, has a long duration of action, and it can be taken at home. A total of 76 participants (37 females and 39 males) were included in the study. The participants were grouped in Group I (n = 51): patients treated with deferasirox; and Group II (n = 25): patients treated with deferoxamine.

Physical and laboratory assessments

Information was obtained from the data recorded from the patients referred to the Thalassemia center. The characteristic features of the patients, past medical and surgical history, duration of receiving blood transfusions, and duration of deferoxamine or deferasirox therapy, were obtained. A blood sample was collected at 8:00 a.m. before the initiation of blood transfusion for measurement hematological indices and the live enzymes. The laboratory tests were carried out in the Thalassemia center (by utilizing the Coulter machine for determination of complete blood count, and Cobas analyzer for determination of liver enzymes). The hematological indices and liver enzymes included red cell count, HB, MCH, MCHC, MCV, blood platelets, serum ferritin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST).

Calculations of scores and indices

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Haematological indices: hemoglobin densities were calculated to identify the associated anemia, whether it is absolute or restrictive iron deficiency anemia, using the following equations:

Mean density hemoglobin/L index (MDHI) = $(\frac{MCH}{MCV}) \times RBC$ (12)

A cutoff value of <1.63 indicates an absolute iron deficiency, while a value of > 1.63 indicates restrictive iron deficiency i.e., the available iron is not utilized by cells, e.g. β-thalassemia.

Mean cell hemoglobin density index (MCHDI) = $\frac{MCH}{MCV}$ (13)

A cutoff value of <0.3045 indicates an absolute iron deficiency, while a value of > 0.3045 indicates restrictive iron deficiency.

The above mentioned hematological indices are used to differentiate iron deficiency anemia from β-thalassemia trait.

Calculation of liver indices: the hepatic enzyme indices that indicate liver fatty degeneration or liver fibrosis were calculated to identify evidence of liver damage using the following equations:

Alanine-to-aspartate aminotransferases ratio = $\frac{\text{Seum ALT}}{\text{Serum AST}}$ (14)

A cutoff value of more than 1, indicates fatty liver degeneration, taking the upper normal limits of ALT or AST is 40 I.U./L.

Aspartate-to-alanine aminotransferase ratio = $\frac{\text{Serum AST}}{\text{Serum ALT}}$ (15)

A cutoff value of more than 1 indicates liver fibrosis.

The fibrosis -4 (FIB-4) score = $\frac{\text{Age x serum AST}}{\text{Platelet count x } \sqrt{\text{ALT}}}$

Aspartate-to-platelet ratio index (APRI) = $[\frac{\frac{\text{Serum AST}}{\text{Upper normal limit serum AST}}}{\text{Platelet count}}]$ x 100

Cutoff values of FiB-4 (>0.26) and APRI score (>0.5) were used as evidence of liver fibrosis in children (16).

Ethical Consideration

The study protocol was approved by the Institutional Ethics & Research Registration Committee (No. PH 100-23; date: June 12, 2023).

Statistical analysis

SPSS (IBM Corporation, Chicago, USA), version 25.0 was used to perform the analyses. The data was not distributed normally as the results of the Shapiro-Wilk test showed significant differences. The data was displayed in the form of numbers, percentages, median, and interquartile (Q1-Q3). The categorical data represented by frequency were analyzed using the Chi-square test, and continuous data represented by median were analyzed using a non-parametric test, the two-tailed Mann-Whitney U-test. The correlation between serum ferritin as a continuous variable and other parameters was assessed using Spearman's correlation analysis. P-values of <0.05 were considered significant.

Results

Demographic characteristics of patients

Table I shows the characteristics and hematological indices. There were non-significant differences between Groups I and II in the median values of age, sex, duration of disease, and previous history of splenectomy. Participants in Group II had a significantly shorter period of treatment compared with the corresponding period in Group I.

Hematological indices of patients

The median values of HB, MCH, MCHC, and blood platelets were non-significantly higher in Group II compared with the corresponding values in Group I, while the MCV value was significantly higher in Group II than Group I (79.8 fL versus 77 fL, respectively).

Indicators of iron storage status

Table II shows that the median serum ferritin level was significantly higher in Group II, which was 1.9 fold higher than

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in Group I. There were no significant differences between Group I and Group II in the median values of MDHI and MCHDI, which showed that the participants had evidence of both absolute and restrictive iron deficiency anemia. The MDHI value in both groups is lower than the cutoff value of 1.63 groups, and the MCHDI value is higher than the cutoff value of 0.3045.

Liver indices

Table III shows the changes in the liver enzymes, FiB-4 score and APRI that indicate structural and functional changes in the liver. The data were analyzed in terms of the frequency of participants who had abnormally high levels and the magnitude of each variable represented by the median value. A significantly higher number of Group II participants had serum levels of ALT and AST greater than 40 I.U./L compared with the corresponding values in Group I. A significantly higher number of Group I patients (72.5%) had AST-to-ALT ratios greater than one, while a significantly higher frequency (56%) of Group II patients had ALT-to-AST ratios greater than one. There were no significant differences between Groups I and II in the frequency of patients who had FiB-4 score and APRI scores greater than the cutoff values of 0.26, and 0.5, respectively. A higher AST-to-ALT ratio and Fib-4 score were found among Group I compared with Group II patients.

Correlations between serum ferritin levels and other laboratory indices

Table IV shows that there is a relationship between red blood cell parameters and serum ferritin level in both Groups I and II, but it is not significant, which shows evidence of restrictive anemia. Only in Group I, a significant correlation between serum ferritin level and liver enzymes was observed. Here, serum ferritin level in Group I was directly and significantly correlated with the ALT to AST ratio and APRI indices, as respective indicators of fatty degeneration and liver fibrosis ($r = 0.519$, $df= 49$, $p < 0.001$, $r = 0.518$ $df = 49$, $p<0.001$, respectively).

In Group II, a positive but not significant correlation was observed between these indicators and serum ferritin level.

Table I: The characteristics and the hematological indices of the participants

Variables	Group I (n=51)	Group II (n=25)	p-value
Sex (Female: Male)	27: 24	10: 15	0.335
Age (year)	7.0 (5.0-10.0)	5.0 (4.5-7.0)	0.115
History of splenectomy	2	2	0.594
Duration of disease (year)	7.0 (5.0-10.0)	5.0 (4.0-7.0)	0.101
Duration of using drugs	4.0 (3.0-7.0)	2.0 (1.5-4.0)	0.013
Red cell count ($\times 10^6/mm^3$)	2.96 (2.78-3.26)	3.0 (2.825-3.185)	0.960
Hemoglobin (g/dL)	8.2 (7.5-8.6)	8.6 (7.9-9.2)	0.068
Mean corpuscular volume (fL)	77.0 (74.0-80.0)	79.8 (76.1-81.8)	0.026
Mean corpuscular hemoglobin (pg)	27.3 (26.1-28.3)	27.8 (27.1-28.8)	0.068
Mean corpuscular hemoglobin concentration (g/dL)	35.0 (34.2-36.1)	35.1 (34.1-35.5)	0.539
Platelet count ($\times 10^3/mm^3$)	318.0 (239.0-400.0)	361.0 (243.0-648.0)	0.306

The results are presented as number and median (interquartile). The p-values were computed by Mann-Whitney U-test. Group I: patients treated with deferasirox, and Group II: patients treated with deferoxamine.

Table II. Laboratory indices of indicators of iron status

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Variables	Group I (n=51)	Group II (n=25)	p-value
Serum ferritin (µg/mL)	1654 (1050-3566)	3144 (1596-4962)	0.037
Mean density hemoglobin/L index	1.082 (0.992-1.125)	1.055 (0.919-1.118)	0.547
Absolute iron deficiency (< 1.63)	51	23	
Restrictive iron deficiency (> 1.63)	0	0	
Mean cell hemoglobin density index	0.351 (0.345-0.362)	0.353 (0.343-0.355)	0.562
Absolute iron deficiency (<0.3045)	0	2	
Restrictive iron deficiency (>0.3045)	51	23	

The results are presented as median (interquartile). The p-values were computed by Mann-Whitney U-test. Group I: patients treated with deferasirox, and Group II: patients treated with deferoxamine.

Table III: Liver enzymes and their derived scores that indicate liver fibrosis

Variables	Group I (n=51)	Group II (n=25)	p-value
Serum ALT (I.U) level	27.0 (15.0-119.0)	53.0 (27.0-73.5)	0.678
Number of patients with a serum level of >40 I.U./L	20	17	0.018
Serum AST (I.U) level	40.0 (30.0-103.0)	51.0 (37.0-63.5)	0.996
c a serum level of >40 I.U./L	23	19	0.011
AST-to-ALT ratio	1.407 (0.862-1.933)	1.143 (0.767-1.415)	0.048
Number of patients with of >1.0	37	11	0.015
ALT-to-AST ratio	0.711 (0.517-1.160)	0.875 (0.710-1.303)	0.048
Number of patients with of >1.0	14	14	0.015
FiB-4 score	0.187 (0.124-0.284)	0.131 (0.074-0.187)	0.015
Number of patients with of> 0.26	13	4	0.315
Aspartate to platelet ratio index	0.376 (0.245-0.725)	0.336 (0.218-0.590)	0.253
Number of patients with of > 0.5	14	7	0.960

The results are presented as number and median (interquartile). The p-values were computed by Mann-Whitney U-test for median values, and Chi-square test for frequency data. Group I: patients treated with deferasirox, and Group II: patients treated with deferoxamine.

Table IV: Bivariate correlations between serum ferritin and haematological, and hepatological indices

Variables	Group I (n=51)	Group II (n=25)
Hemoglobin (g/dL)	0.112 (0.433)	-0.076 (0.718)
Mean corpuscular volume (fL)	0.130 (0.362)	0.016 (0.939)
Mean corpuscular hemoglobin (pg)	0.177 (0.213)	-0.246 (0.235)
Mean corpuscular hemoglobin concentration (g/dL)	0-.061 (0.671)	-0.339 (0.097)
Mean density hemoglobin/L index	0.020 (0.888)	-0.111 (0.598)
Mean cell hemoglobin density index	0.041 (0.773)	-0.271 (0.190)
Platelets count ($\times 10^3/mm^3$)	0.024 (0.866)	0.048 (0.818)
Alanine aminotransferase (I.U)	0.562(<0.001)	0.387 (0.056)
Aspartate aminotransferase (I.U)	0.469 (0.001)	0.420 (0.037)
Aspartate-to-alanine aminotransferase ratio	-0.519 (<0.001)	-0.239 (0.249)
Alanine-to-aspartate aminotransferase ratio	0.519 (<0.001)	0.239 (0.249)
Fibrosis-4 score	-0.147 (0.302)	0.142 (0.497)
Aspartate aminotransferase-to-platelet ratio	0.518 (<0.001)	0.186 (0.373)

The results are presented as correlation factor (p-value). P-values (between brakets) were calculated using two-tailed Spearman's correlation test. Group I: patients treated with deferasirox, and Group II: patients treated with deferoxamine.

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Discussion

It was found in this study that both deferasirox and deferoxamine could potentially cause changes in hematological and liver indices in thalassemia patients receiving blood transfusions. Notably, deferoxamine treatment was associated with significantly elevated serum ferritin levels and liver enzymes, along with reduced liver fibrosis indices. Interestingly, there were no significant correlations between serum ferritin levels and liver fibrosis indices in deferoxamine-treated group. Because deferoxamine has a shorter duration of action than deferasirox, some pediatricians prefer to start with deferoxamine and subsequently switch to deferasirox. β-thalassemia major patients adhered better to deferasirox than to deferoxamine therapy, which is another reason to switch to deferasirox (17). For that reason, the duration of deferoxamine was shorter than in patients treated with deferasirox.

In Group II, the median value of MCV was significantly higher than the corresponding value in Group I, indicating that deferoxamine has a potential favourable impact on the anemia of thalassemia besides its property of chelating iron. Deferoxamine reduces the iron overload unevenly in the body organs and blood elements, which improving the utilization of iron by red cells and thus increasing the MCV values (18, 19). This suggests that erythroid response can occur when ICAs are used, which is consistent with a previous study that found erythroid response was occurred in certain patients with myeloproliferative neoplasm who were treated for iron overload due to repeated blood transfusions (20). There is evidence that deferasirox elevates Hb levels and blood platelet count (21). Our findings revealed no significant differences in the effects of defersirox and deferoxamine on Hb and platelet count.

According to Table II, significantly higher serum ferritin levels in the deferoxamine-treated group (Group II) compared to the deferasirox-treated group (Group I) may be due to a significantly shorter period of deferoxamine medication. This observation is consistent with earlier studies that show that using ICSs for a longer period of time and more frequently lowers iron overload (22). Also, the baseline ferritin level is also a determinant factor for the elimination rate of iron by deferoxamine (22).

As shown in Table II, both medications changed hemoglobin density, and their usage will conceal one of the diagnostic criteria of thalassemia in which their patients had a MDHI value of less than 1.63. This observation suggests that both types of anemia persisted following the use of ICAs, the first being restrictive iron deficiency anemia (the MCHDI > 0.3045), which is related to β-thalassemia, and the second being absolute iron deficiency anemia (the MDHI <1.63), which is related to the ICAs (23).

Both deferoxamine and deferasirox had a detrimental effect on the liver. Significant increases in ALT and AST magnitudes were seen in patients treated with deferoxamine compared to patients treated with deferasirox. Others had previously found that both ALT and AST levels were elevated in thalassemia patients treated with deferoxamine (24). A ratio of AST-to-ALT of > 1 as an indicator of liver fibrosis is a feature of deferasirox therapy, while a ratio of ALT-to-AST of > 1 as an indicator of fatty liver degeneration is a feature of deferoxamine therapy. In addition, the median score of FiB-4 as an indicator of liver fibrosis is a feature of deferasirox. A previous study found that long-term (over 3 years) deferasirox

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medication stabilizes liver fibrosis (based on the histopathological assessment) in thalassemia patients with hepatitis C (25). This disparity in our findings could be attributed to the methodologies used to assess liver fibrosis, as well as the concurrent disease of viral hepatitis. Previous research revealed that deferasirox had toxic effects on the liver, and its hepatic toxicity was significantly and positively linked with serum ferritin, as shown in Table IV (26). Furthermore, there are substantial positive correlations between serum ferritin and liver enzymes, demonstrating that hepatotoxicity is attributed to high ferritin levels in thalassemia patients treated with blood transfusion (27). As an outcome, paediatricians advised for lowering serum ferritin levels to 1,500 □g/L in patients with thalassemia who were managed with repeated blood transfusion in an attempt to limit liver damage (28), but as this study demonstrated, this level is not easy to maintain. The strength of this study is these findings are being reported for the first time.

Conclusion

Both deferoxamine and deferasirox were indicated to reduce iron overload, but their effects on red cell components, serum ferritin, and liver enzymes varied. Patients treated with deferasirox had a significant higher hepatic fibrosis scores than those treated with deferoxamine, while patients treated with deferoxamine have significant higher alanaine-to-aspartate ratio, and circulating ferritin levels.

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Author contributions

Concept –M.A-N.; Design – M.A-N., R.H., R.R.; Supervision –M.A-N.; Resources – M.A-N., R.H; Materials – R.H., R.R; Data Collection and/or Processing – R.H., R.R.; Analysis and/or Interpretation M.A-N; Literature Search – M.A-N., R.H., R.R.; Writing – M.A-N.; Critical Reviews – M.A-N., R.H., R.R.

Conflict of interest

The authors declare no conflict of interest.

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