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ORIGINAL ARTICLE

Effect of Iron Chelator on Renal Function in Thalassemia Patients who Undergo Regular Transfusion

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ABSTRACT

Background: The thalassemia family of genetic disorders is characterized by an abnormal synthesis of the hemoglobin chain, resulting in chronic anemia in some people and clinically asymptomatic in others. There have been very few studies conducted on the effects of thalassemia on the kidneys, which typically included patients treated with deferoxamine having both glomerular and tubular dysfunction.

Objective: This research aimed to determine whether kidney dysfunction is observed in young thalassemic individuals manipulating both conventional and primitive markers of kidney dysfunction, and to associate the results to the use of iron chelation therapy.

Methods: We measured serum cystatin C (Cys C), tubular phosphorus reabsorption (TPRA), fractional sodium excretion (FNE), and 2-microglobulin, urine calcium, protein, and glucose levels in addition to the usual renal biochemistry.

Results: A whole of 42 individuals, ranging in age from 4 to 23, were included in this study and were split into two groups for study (group A taking deferoxamine alone, and group B taking deferiprone coupled with deferoxamine). An increased Cys C level (36%) and proteinuria (24%) were seen in a large percentage of patients, as were tubulopathy with hypercalciuria (35.5 %) and point out 2-MG excretion (33.5 %).

Conclusion: Patients with -thalassemia seem to suffer from renal dysfunction even when they are young, so it is important to monitor early signs of renal dysfunction. There is a need for further research into the effect of novel chelators on parameters tubular function.

Keywords: Deferiporin, iron chelator, thalassemia, Peshawar, dfo

INTRODUCTION

The genetic condition known as Thalassemia major results from a genetic defect in the production of chain of hemoglobin. This leads to a chronic state of anemia. Among a wide variety of genetic defects in hemoglobin synthesis, it is the most severe form, where life must be maintained by regular blood transfusions (1).Despite the prolonged life spans associated with transfusion therapy, a lack of the procedure may result in unequal accumulation of iron in various organs, since there is no physiological excretion mechanism for iron. Patients with untreated iron deposition die during their second decade of life, as it primarily affects the heart, liver, and endocrine glands (2, 3).Consequently, lifelong chemotherapy is an important aspect of -thalassemia patients' treatment, as it extends their lives and considerably increases their quality of life. The deferroxamine (DFO) has been widely used for almost four decades as a parenteral iron chelator, with both an established benefit profile and a clear set of limitations(4, 5). In recent years, two orally active chelators, deferasirox (DFRA), and deferiprone have been extensively used as effective alternatives to intravenous chelation treatments(4, 6, 7) . It is important to note that although there has been a lot of research on the complications of thalassemia, there has been little data on how it affects the kidneys(8). In the limited reports that have been made on the subject of renal dysfunction among patients with thalassemia, most of them referred to patients receiving dialysis(9-11).Additionally, they did not assess any of the rather recent biomarkers of kidney function, i.e., as urinary 2 -micro-globulin or serum cystatin C. In this study, common and advanced biomarkers will be used along with possible correlation with iron chelation therapy in individuals with thalassemia major to screen for glomerular and tubular dysfunction.

METHODS AND MATERIALS

Study participants comprised of included forty-two individuals (22 males and 20 females). The patients were also regularly chelated in addition to receiving regular transfusions. Various demographic characteristics were collected from all the patients, including age, gender, transfusion duration, number of transfusions, and iron chelation regimen. All the 42 participants age ranged from four to twenty-three years.We measured anaverage hemoglobin value of 9.3 g/dl and a average ferritin values of 1,401 ng/ml. A total of 28 patients (group A) received DFRA, while 14 patients (group B) received a combination of deferiprone and DFO for their iron chelation treatments. The dose of DFRA was 15–35 mg/kg/day orally, and the dose for combination therapy was 11–48 mg/kg/day subcutaneously, 5 times per week, and 60–80

mg/kg/day orally. The control group consisted of 15 healthy children of the same age group.In addition to the hematological and biochemical tests, blood was collected for the following metabolic tests: calcium, Creatinine, hemoglobin, potassium, phosphate, parathyroidhormone, sodium, magnesium, acid-base balance, urea, and whole bicarbonate levels. The following blood components were determined from 24-hour urine samples: sodium, albumin, Cr, potassium, calcium, and phosphorus. Serum cystatin C (Cys C) and urinary 2-MG, all are primitivebiomarkers of renal and tubular dysfunction, were measured in addition to conventional renal biochemistry. Rate nephelometry was used to examine serum Cys C. Urine 2-MG levels were measured using rate nephelometry. Thirty-four out of 42 patients underwent a renal ultrasound. Formulas were used to calculate sodium and calcium fractional excretion, as well as tubular reabsorption. In order to conduct the statistical analysis, SPSS Version 25 was used. We defined significant results as those with a p value less than 0.05 depending on the data.

RESULTS

In comparison with controls, all patients had normal blood biochemistry and metabolism p>0.05. There were the following parameters: total bicarbonates, urea, sodium, calcium, phosphate, magnesium, acid-base balance, serum Cr, and potassium and total proteins. The serum Cr, CrC, and eGFR did not differ significantly from the control groups. CrC, eGFR, and serum Cr were respectively 137 +/- 25.67, 128 +/- 17.45 ml/min/1.73 m2 and 0.7 +/- 0.16 mg/dl.There was only one patient with a reduced eGFR of 74 ml/min/1.73 m2. A significant difference in serum values of Cys C was found in the participants cohort competed to the control cohort (0.89 +/- 0.21 and 0.67 +/- 0.2862 mg/l, continuously, p = 0.001). Particularly, 15/42, or 36%, of the patients had abnormally high Cys C levels in their serum. When compared with children with normal levels of Cys C, children with elevated levels exhibited high 2 -MG values (p = 0.017). In 2-microglubulin levels of urine, Cys C correlation was significant (r = 0.325, p = 0.032). Cys C levels, however, were not associated with age, ferritin, eGFR,iron chelation therapy, proteinuria,CrC, and urine Ca^{+2}values (p 0.05). Table 1 compares average value of urine and blood variables between the two study groups regarding iron chelation therapy. Comparing erythrocyte volume transfusions between groups A and B (p = 0.948). In comparison with patients in group B, participants in group A were younger (p = 0.007). Moreover, patients in group A had elevated blood ferritin values (p = 0.033), elevated urinary Ca^{+2} (p = 0.045 and p = 0.001, continuesly), lowered FE sodiumvalues (p = 0.04) and lowered serum Cr values (p = 0.011).

Table 01: Shows association between thalassemia, and iron chelator and associated biomarkers

Parameters	DFRA (Group A)	Deferiprone DFO (Group B)	Control	P^1	P^2	P^3
Age	6.75	12.10	12.66	0.007	0.006	NS
Hemoglobin	9.4	9.2	13.2	NS	0.0001	0.0001
Transfusion	16.3	17.6	-	NS	-	-
Serum Creatinine	0.6	0.8	0.7	0.011	0.045	NS
Serum Ferritin	1519	1147	38.5	0.03	0.0001	0.0001
Serum Urea	35	34	37	NS	NS	NS
Urine Phosphate	95	96	96	NS	NS	NS
FE Sodium	0.7	1.411.21	1.21	0.04	0.03	NS
Cystatin C	0.92	0.84	0.67	NS	0.0001	0.001
Urine Protein	250	210	79	NS	0.007	0.011
2-MG	5	0.25	0.2	0.001	0.0001	0.009
eGFR	127	122	131	139	NS	NS
Urine Calcium	6	4	1.8	0.045	0.0001	0.0001
Creatinine Clearance	135	131	139	NS	NS	NS

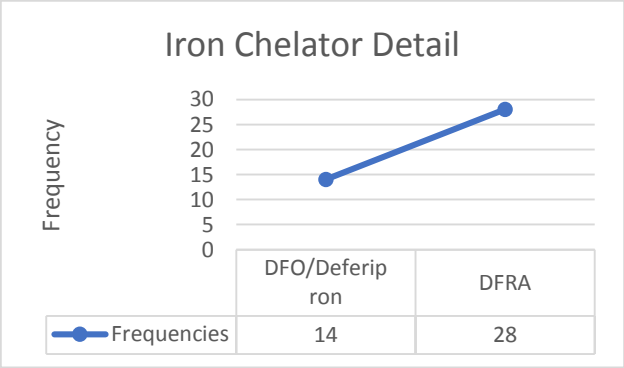

Figure. 01: Shows frequencies of different iron Chelators

DISCUSSION

Unlike other organs affected by the disease, the kidneyengrossment of thalassemia affected individuals was less elaborated than other complications like heart disease or endocrine disorders. Furthermore, the reports were based on patients undergoing DFO and used markers that do not indicate renal changes at an early stage(7, 12). There have been several studies showing the existence of renal dysfunction in thalassemic individuals, caused by chronic anemia. In thalassemic patients, proximal tubular dysfunction has been demonstrated to be due to persistent anemia, iron strain, and/or excessive DFO consumption(13).Current study comprised of forty-two younger thalassemia major affected individuals, who received chelation therapy at conventional dosage as well as regular blood transfusions. Additionally, to the usual kidney indexes, such as cystatin clearance and 2-microglobulin, earlier markers were also evaluated(14, 15). There was impaired glomerular and tubular renal function in the study.Further, the results indicate that the patient had impaired renal function due to high Cys C levels (36 percent), momentous tubulopathy due to hypercalciuria (35.5 percent), and urinary defecation of 2 - MGs (33.5

percent), along with glomerular dysfunction due to proteinuria (24 percent). Ferritin, although higher than 1,000 ng/ml in more than half of the study subjects (54.5%), was not an independent predictor of either glomerular dysfunction or tubular dysfunction(16, 17). Although ferritin levels may not adequately reflect hemosiderosis, and iron chelation may not be sufficient to remove deposited iron in renal tubules, it is well understood that these factors cannot be determined. A standard measurement of electrolytes, urea, and Cr was found to be normal in all the participants in the present study [12]. In contrast to controls, CrC and eGFR were not significantly different (p 1 0.05). In the study by Koren et al. [11], 40% of patients with thalassemia major suffered a significant decline in GFR after receiving DFO subcutaneously and another 40% experienced a mild decrease. It has been shown, however, that DFO nephrotoxicity is dose dependent(18).

Among the patients in this study, only one had a reduced glomerular filtration rate of 74 ml/min/1.73 m2. In addition to conventional DFO dosage, the participants have a lower ferritin value (458 ng/ml). As serum Cr is influenced by factors that are irrelevant to kidney function, i.e., ingestion of protein,hepatitis, inflammatory illnesses andmuscle mass, it is considered a poor indicator of kidney function changes(19, 20).In addition, Creatinine is partly secreted by renal tubules and is a frequent overestimation of GFR. In order to screen out kidney function abnormality at an initial stage an broadinvestigation is being steered for a serum marker that can reveal it. Studies have shown that serum Cys C is superior to serum Cr in evaluating GFR, especially when GFR is reduced slightly. In all nucleated cells, Cys C is a proteinase inhibitor that is age-independent and gender intolerant.

There has been controversy over DFO's role, while the potential benefits of chelating agents remain to be seen. Even though patients on DFRA were younger, they presented with higher levels of 2 MG and hypercalciuria than those on combination therapy. Due to their high ferritin levels, it is difficult to determine whether the chelator had a direct impact on tubular dysfunction or whether iron overload was the culprit. Even though DFO was administered in much minor doses and in a subcutaneous manner associated to previous results where it was administered intravenously as monotherapy, an increased level of FE Na can also be attributed to DFO treatment.After discontinuing the drug, it has been reported that the effect reverses. In this study, serum Cys C and urine 2-MG were found to be markers of early kidney damage (tubular and glomerular, respectively), while calciuria and proteinuria demonstrated both acute and chronic damage. A chronic anemia and iron overload are believed to contribute to proteinuria and microalbuminuria, according to the literature.

CONCLUSION

Thalassemia patients exhibit renal disorders even when they are young. This patient cohort should be monitored for early markers because kidney failure may not screened out by routine tests. A further investigation of new chelators is needed to determine their effects on tubular function parameters such as urinary Ca^{+2} and 2-MG excretion.

REFERENCES

1. Demir A, Yarali N, Fisgin T, Duru F, Kara AJPI. Most reliable indices in differentiation between thalassemia trait and iron deficiency anemia. 2002;44(6):612-6.
2. Hoffmann JJ, Urrechaga E, Aguirre UJCC, Medicine L. Discriminant indices for distinguishing thalassemia and iron deficiency in patients with microcytic anemia: a meta-analysis. 2015;53(12):1883-94.
3. Canatan D, Akdeniz SKJMjoh, diseases i. Iron and ferritin levels in saliva of patients with thalassemia and iron deficiency anemia. 2012;4(1).
4. Neufeld EJJH, the American Society of Hematology Education Program Book. Update on iron chelators in thalassemia. 2010;2010(1):451-5.
5. Nick H, Acklin P, Lattmann R, Buehlmayer P, Hauffe S, Schupp J, et al. Development of tridentate iron chelators: from desferrithiocin to ICL670. 2003;10(12):1065-76.
6. Cohen AR, Galanello R, Piga A, De Sanctis V, Tricta FJB. Safety and effectiveness of long-term therapy with the oral iron chelator deferiprone. 2003;102(5):1583-7.
7. Kersten M, Lange R, Smeets M, Vreugdenhil G, Roozendaal K, Lameijer W, et al. Long-term treatment of transfusional iron overload with the oral iron chelator deferiprone (L1): a Dutch multicenter trial. 1996;73(5):247-52.
8. Seyedifar M, Dorkoosh FA, Hamidieh AA, Naderi M, Karami H, Karimi M, et al. Health-related quality of life and health utility values in beta thalassemia major patients receiving different types of iron chelators in Iran. 2016;10(4):224.
9. Sharma RN, Pancholi SJJCPR. Oral iron chelators: A new avenue for the management of thalassemia major. 2010;1:1-7.
10. Szuber N, Buss JL, Soe-Lin S, Felfly H, Trudel M, Ponka PJEh. Alternative treatment paradigm for thalassemia using iron chelators. 2008;36(7):773-85.
11. Schmidt PJ, Racie T, Westerman M, Fitzgerald K, Butler JS, Fleming MDJAjoh. Combination therapy with a T mprss6 RNA i-therapeutic and the oral iron chelator deferiprone additively diminishes secondary iron overload in a mouse model of β-thalassemia intermedia. 2015;90(4):310-3.
12. Rao SS, Portbury S, Lago L, Bush AI, Adlard PAJJoAsD. The iron chelator deferiprone improves the phenotype in a mouse model of tauopathy. 2020;77(2):753-71.
13. Kontoghiorghe CN, Kontoghiorghes GJJDD, Development, Therapy. Efficacy and safety of iron-chelation therapy with deferoxamine, deferiprone, and deferasirox for the treatment of iron-loaded patients with non-transfusion-dependent thalassemia syndromes. 2016;10:465.
14. Saeki I, Yamamoto N, Yamasaki T, Takami T, Maeda M, Fujisawa K, et al. Effects of an oral iron chelator, deferasirox, on advanced hepatocellular carcinoma. 2016;22(40):8967.
15. Taher AT, Saliba AN, Kuo KH, Giardina PJ, Cohen AR, Neufeld EJ, et al. Safety and pharmacokinetics of the oral iron chelator SP-420 in β-thalassemia. 2017;92(12):1356-61.
16. Gomber S, Jain P, Sharma S, Narang MJIp. Comparative efficacy and safety of oral iron chelators and their novel combination in children with thalassemia. 2016;53(3):207-10.
17. Yassin MA, Soliman AT, De Sanctis V, Hussein RM, Al-Okka R, Kassem N, et al. Jadenu® substituting Exjade® in iron overloaded β-thalassemia major (BTM) patients: a preliminary report of the effects on the tolerability, serum ferritin level, liver iron concentration and biochemical profiles. 2018;10(1).
18. Peyam S, Bansal DJIJoP. Dual Oral Iron Chelation in Thalassemia: Need for Robust Evidence. 2021;88(4):319-21.
19. Sousa L, Oliveira MM, Pessôa MTC, Barbosa LAJCCA. Iron overload: Effects on cellular biochemistry. 2020;504:180-9.
20. Rostoker G, Vaziri ND, Fishbane SJD. Iatrogenic iron overload in dialysis patients at the beginning of the 21st century. 2016;76(7):741-57.