Original Article

Serum Ferritin Status and Chelation Therapy of Children and Adolescents with Transfusion Dependent Thalassemia Major in Mirpur, AJK

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ABSTRACT

Objective: To assess the serum Ferritin levels and chelation therapy in transfusion dependent Thalassemia major children and adolescents in Divisional Headquarters Teaching Hospital, Mirpur, AJK.

Study Design: Descriptive Observational Study

Place and Duration of Study: This study was conducted at the Thalassemia Center of Divisional Headquarters Teaching Hospital, Mirpur, AJK from Oct, 2019 to March, 2020.

Materials and Methods: After taking permission from hospital ethics committee, children with transfusion dependent Thalassemia aged up to 18 years were added in the study after informed written consent. Blood samples were sent for Serum Ferritin levels. Serum Ferritin measurement was done by indirect ELISA kit. Chelation therapy was assessed in terms of Deferasirox Tablets and Desferrioxamine injection. Data were analyzed on SPSS 20 and the correlation between age, gender, serum Ferritin level and chelation therapy were checked.

Results: A total of 100 children registered with Thalassemia center, Divisional Headquarters teaching hospital, Mirpur were included in this study. There were 55 (55%) males and 45 (45%) females. There were 18 (18%) children between 1-3 years, 20 (20%) in 4-5 years, 17 (17%) in age group 6-8 years, 30(30%) in 9-15 years and 15 (15%) above 15 years of age. Serum Ferritin monitoring revealed 29 (29%) children having Serum Ferritin level between 500-2500ng/dl, 16 (16%) between 2501-3500ng/dl, 19 (19%) between3501-5000ng/dl, 26(26%) between 5001-9000ng/dl and 10 (10%) were having above 9000ng/dl. Maximum children (29%) were found in 500-2500ng/dl serum Ferritin. Majority (66%) was taking chelation as compared to 34% who were not taking any chelation. A strong association was present between Child's age and serum Ferritin levels with P-value < 0.001. With increasing age, more number of children were taking chelation as compared to younger age (93.33%) at 15 years of age as compared to (45.00%) at 4-5 years of age. Comparing Gender versus chelation revealed that more females i.e. 33 (73.33%) out of 45 were taking chelation as compared to males (60%) taking chelation. It was observed that chelation percentage increased with increasing Ferritin level with P-value < 0.004.

Conclusion: The average serum Ferritin levels are significantly raised as compared to the normal permissible levels in these patients. This is further made worse by the fact that around one third of them are not receiving any kind of iron chelation therapy.

Key Words: Thalassemia, Ferritin, Chelation, AJK

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INTRODUCTION

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Thalassemia is one of the genetically acquired disorders of defective globin chain synthesis, resulting in imbalance between the alpha and beta globin chains present in Hemoglobin[1]. Globally around 70,000 new children are born with different types of Thalassemia annually.[2]Thalassemic children who are transfusion dependent generally require monthly RCC (red Cell concentrate) transfusions resulting in excessive iron load on the body.

Every single unit of packed RCC produces 200mg of free iron in human body.[3]

During normal condition, iron binds with a carrier protein Transferrin which transports iron in various tissues. However, if there is excessive iron in the body due to any cause, Transferrin becomes fully saturated leaving free iron in blood circulation. Free iron radicals

are highly toxic and generate reactive oxygen forms which can badly damage various organs.[4] Vital organs damage like liver, heart and endocrine glands is the leading cause of complications, disability and even death of children in thalassemia.[5] There are many investigations both invasive as well as non-invasive to check iron status of Thalassemia patients, however serum Ferritin is the readily available and cheap method. Iron Chelation therapy (ICT) is started in all patients generally after 1-2 years of RCC transfusions with a target to keep serum Ferritin < 1000 µg/l. Excessively high values of serum Ferritin crossing 2500 µg/l can lead to vital organ damage especially heart, liver and endocrine glands.[6] Regular blood transfusions in Thalassemia patients demand continuous Iron Chelation Therapy (ICT) to avoid the excessive iron load which can lead to cardiomyopathy and decreased cardiac output. This can even decrease total life expectancy of these patients and may have high mortality. [7] On the other hand, this ICT therapy is very expensive and time consuming as well and put another financial burden on these patients. Deferasirox, a novel oral chelator, although effective and easy to administer but it is quite expensive and poses a considerable financial risk as it has to be given daily and lifelong.[8]Deferoxamine (DFE), the traditional ICT, being given parenterally is being used for more than 4 decades. It is found to be quite effective iron chelator but needs assistance as well as long time for administration.[9] It is found that Thalassemia patients are still unable to attain the optimum levels of Serum Ferritin so mostly a combination of chelators is used to control serum Ferritin levels.[10]

MATERIALS AND METHODS

In this study, we enrolled children suffering from Transfusion dependant Thalassemia aged less than 18 years registered with Thalassemia center of Divisional headquarters teaching hospital. A well-informed written consent was taken. Patients who were undergoing regular blood transfusions monthly for last 2 years were recruited in the study. Blood samples were sent for Serum Ferritin assays. Serum Ferritin levels were done by indirect ELISA kit. Chelation therapy was assessed in terms of Deferasirox Tablets as well as Deferoxamine injections. Data were analyzed on SPSS 20 and the association between age, gender, serum Ferritin level and whether taking chelation therapy or not were established.

RESULTS

A total of 100 children registered with Thalassemia center, Divisional Headquarters teaching hospital Mirpur were included in this study. There were 55 (55%) males and 45 (45%) females. Age was divided in further subgroups for analysis purpose. There were 18 (18%) children between 1-3 years, 20 (20%) in 4-5 years, 17 (17%) in age group 6-8 years, 30(30%) in 9-15 years and 15 (15%) above 15 years of age.

All Thalassemia patients were having high serum Ferritin. Serum Ferritin monitoring revealed 29 (29%) children having Serum Ferritin level between 500-2500ng/dl, 16 (16%) between 2501-3500ng/dl, 19 (19%) between3501-5000ng/dl, 26(26%) between 5001-9000ng/dl and 10 (10%) were having above 9000ng/dl. Maximum children (29%) were found in 500-2500ng/dl serum Ferritin.

Table No.1: Serum Ferritin Status:

		Frequency	Percent	Cumulative Percent
Valid	500-2500	29	29.0	29.0
	2501-3500	16	16.0	45.0
	3501-5000	19	19.0	64.0
	5001-9000	26	26.0	90.0
	>9000	10	10.0	100.0
	Total	100	100.0	

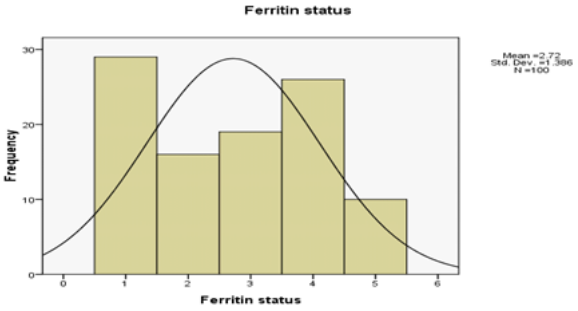

Figure No. 1: Ferritin Status with Frequency

Table No.2: Chelation status

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	66	66.0	66.0	66.0
	No	34	34.0	34.0	100.0
	Total	100	100.0	100.0	

The statistical analysis revealed a strong association between Child's age and serum Ferritin levels with P-value < 0.001.

Table No.3: Child's Age * Ferritin status Cross – tabulation

Ferritin Level		500-2500 ng/dl	2501-3500 ng/dl	3501-5000 ng/dl	5001-9000 ng/dl	>9000 ng/dl	total
Child's Age	1-3yr	8	6	4	0	0	18
	4-5Yr	10	3	4	2	1	20
	6-8yr	3	2	4	5	3	17
	9-15yr	5	4	4	15	2	30
	15yr	3	1	3	4	4	15
Total		29	16	19	26	10	100

As far as Chelation Status was concerned, Majority (66%) was reportedly taking chelation in the form of tab. Deferasirox and Injection Desforaximine as compared to 34% who were not taking any chelation despite counseling.

Table No.4: Chi-Square Tests

	Value	Df	Asymp. Sig. (2-sided)
Pearson Chi-Square	33.779[a]	16	.006
Likelihood Ratio	37.284	16	.002
Linear-by-Linear Association	17.923	1	.000
N of Valid Cases	100		
• 19 cells (76.0%) have expected count less than 5. The minimum expected count is 1.50.			

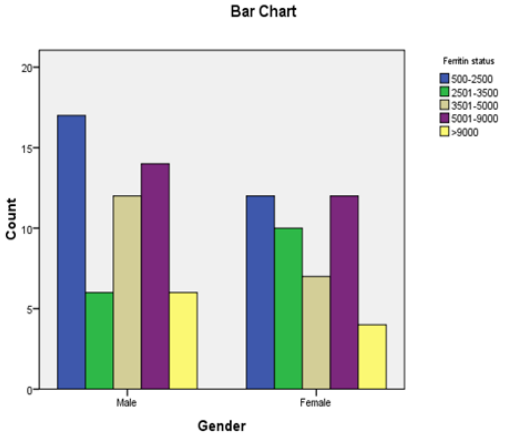

Figure No.2: Association of Gender with Ferritin level

Males were having high serum ferritin levels as compared to female children in our study.
Association of age of child with chelation:

Table No.5: Child's Age * chelation status Cross Tabulation

Chelation status		yes	No	Total
Child's Age	1-3yr	10	8	18
	4-5Yr	9	11	20
	6-8yr	11	6	17
	9-15yr	22	8	30
	15yr	14	1	15
Total		66	34	100

Table No.6: Ferritin status * chelation status Cross Tabulation

Chelation Status		Yes	No	Total
Ferritin status	500-2500	14	15	29
	2501-3500	11	5	16
	3501-5000	15	4	19
	5001-9000	18	8	26
	>9000	8	2	10
Total		66	34	100

It was observed that with increasing age, more number of children were taking chelation as compared to younger age (93.33%) at 15 years of age as compared to (45.00%) at 4-5 years of age.
Cross-tabulating Gender versus chelation revealed that more females i.e. 33 (73.33%) out of 45 were taking chelation as compared to males (60%) taking chelation. It was observed that chelation percentage increased with increasing ferritin level with P-value < 0.004. however, there was one exception in 500-2500ng/dl ferritin level.

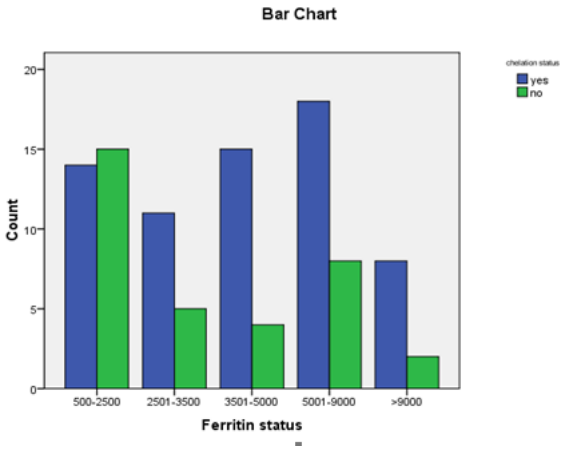

Figure No.3: Ferritin Status with Count

DISCUSSION

It is estimated that the patients suffering from Thalassemia Major receive approximately 20 times higher intake of free iron, so excessive iron load is already anticipated in them. Serum Ferritin assays are the most commonly used method for the estimation of iron overload in these patients as it is simple, cheap and readily available worldwide.[11]A total of 100 children registered with Thalassemia center, Divisional headquarters teaching hospital Mirpur were included in our study. There were 55 (55%) males and 45 (45%) females. Age was divided in further subgroups for analysis purpose. There were 18 (18%) children between 1-3 years, 20 (20%) in 4-5 years, 17 (17%) in age group 6-8 years, 30(30%) in 9-15 years and 15 (15%) above 15 years of age.
All Thalassemia patients were having high serum Ferritin. Serum Ferritin monitoring revealed 29 (29%) children having Serum Ferritin level between 500-2500ng/dl, 16 (16%) between 2501-3500ng/dl, 19 (19%) between3501-5000ng/dl, 26(26%) between 5001-9000ng/dl and 10 (10%) were having above 9000ng/dl. Maximum children (29%) were found in 500-2500ng/dl serum Ferritin and mean Ferritin was 3201ng/dl. These very high values depict ineffective and inadequate degree of chelation and put these children at a high risk of developing complications.

These results were similar to study done by Mishra et al. where 87.4% of the children had significantly higher Ferritin levels. The mean serum Ferritin level was also similar to our study i.e. 2767.52 ng/ml. In that study, around half of the patients had serum Ferritin between 1000 to 2500 ng/ml, while rest of the patients had values above 2500 ng/ml.[12] Serum Ferritin levels were low in a study done in Sri Lanka where Mean serum Ferritin was 1778(± 1458) µg/l and one third of their patients had normal serum Ferritin.[6] A considerably high mean serum Ferritin Value of 9542 ± 782 ng/ml is reported by Al-Zubaidietal which is much higher as compared to our study but no reason has been attributed as a cause of so high Ferritin levels .[12]

In our study, majority (66%) of patients were taking chelation in the form of tab. Deferasirox and Injection Desforaximine as compared to 34% who were not taking any chelation despite counseling. Similar results were shown by Riazetal. in which 58.2% cases were taking chelation and 41.8% were not taking any chelation.[14]

The statistical analysis revealed a strong association between Child's age and serum Ferritin levels with P-value < 0.001. Males were having high serum Ferritin levels as compared to female children in our study but there was no significant statistical analysis. It was observed that with increasing age, more number of children were taking chelation as compared to younger age (93.33%) at 15 years of age as compared to (45.00%) at 4-5 years of age. This is in comparison with Riazetal. who showed that Age and chelation therapy have a significant correlation with Serum Ferritin measurements. This study demonstrated that age in years is directly proportional to the serum Ferritin levels.[14]

Comparing Gender versus chelation revealed that more females i-e 33 (73.33%) out of 45 were taking chelation as compared to males (60%) taking chelation. It was observed that chelation percentage increased with increasing Ferritin level with P-value < 0.004. However, there was one exception in 500-2500ng/dl Ferritin level. Another study by Faruqietal showed similar results with the mean Ferritin value of 6062.61 + 3641.796 ng/ml. He showed that most of the patients were not receiving adequate ICT. And those patients with less optimal ICT were having high serum Ferritin values.[11] This was also in comparison with a study done in Karachi where serum Ferritin levels were comparable to our study (3319.6 ± 1925.8) ng/ml in the chelation group as compared to non- chelation group (5514.8 ± 2383.0) ng/ml.[14]

CONCLUSION

The high serum Ferritin levels in our study strongly supports the rationale of regular monitoring and follow up regarding adequate chelation to minimize iron overload and associated life-limiting complications. We need to create more knowledge and awareness in the Thalassemia patients about the value of monitoring regular serum Ferritin levels. They should be well aware of the consequences and complications of iron overload. Proper chelation of iron overload could improve the quality of life of these patients.

Limitations:

The dose of Deferasirox and Deferoxamine infusions is not ascertained which is a limitation in our study.

Author's Contribution:

Concept & Design of Study:	Saba Haider Tarar
Drafting:	Saba Haider Tarar
Data Analysis:	Waseem Ahmed Khan
Revisiting Critically:	Shakil Asif
Final Approval of version:	Waseem Ahmed Khan

Conflict of Interest: The study has no conflict of interest to declare by any author.

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