Comparison of the Mean Serum Ferritin Levels in Thalassaemia Major Patients after Giving Deferasirox and Deferoxamine

Seema Aftab[1], Amber Kamran[2], Shahina Hanif[3], Ghulam Murtaza[4], Naveen Fatima[5], Noor un Nisa Masqati[6]

Abstract

Objective: To compare the mean serum ferritin levels in thalassaemia major patients after giving deferasirox and deferoxamine. This is a randomised control trial conducted at the Department of Paediatrics, Civil Hospital, Karachi from 29th January 2014 to 28th July 2014.

Methods: A total of 160 patients of either gender, with age between 1 to 14 years, who received blood transfusion at least once a month for one year and had serum ferritin >1000 mcg/L were included. Each enrolled patient was randomly allocated to group-A (deferoxamine) or group-B (deferasirox). Pre- and post-treatment iron profile was done in both groups to assess the iron status in the body. Descriptive statistics were applied to calculate mean and standard deviation for the quantitative variables. Frequencies and percentages were calculated for the qualitative variables. Independent sample t-test was applied to compare mean change in serum ferritin level in both groups. Effect modifiers were controlled by stratification. Paired t-test was also applied post stratification and p-value ≤ 0.05 was considered as significant.

Results: Overall there were 96 male and 64 female patients. The overall mean age of study subjects was 7.54 ± 4.21 years. In the deferasirox group, mean age was 6.35 ± 4.11 years, mean weight was 18.01 ± 6.74 kg, mean height was 102.04 ± 19.48 cm, and mean duration of transfusion was 7.48 ± 3.99 months/year. In the deferoxamine group, mean age was 8.74 ± 3.97 years, mean weight was 20.44 ± 6.77 kg, mean height was 102.19 ± 20.85 cm, and mean duration of transfusion was 8.14 ± 3.55 months/year. In the deferasirox group, before treatment mean serum ferritin level was 1385.73 ± 117.01 mcg/L. After treatment mean serum ferritin level was reduced to 1047.59 ± 117.08 mcg/L. In the deferoxamine group, before treatment mean serum ferritin level was 1362.58 ± 134.42 mcg/L. After treatment mean serum ferritin level was reduced to 1124.36 ± 134.52 mcg/L. Post-treatment the serum ferritin level between two groups was significantly different with $p<0.01$. The mean difference in serum ferritin level in pre- and post-treatment among two groups was highly significant with $p<0.01$.

Conclusion: Deferasirox is an effective, safe and tolerable chelation therapy for the treatment of thalassaemia major with iron overload due to its ability to provide constant chelation coverage and potential to improve compliance.

Keywords: Ferritin, thalassemia major, chelation therapy, deferasirox, deferoxamine.

Citation: Aftab S, Kamran A, Hanif S, Murtaza , Naveen Comparison of the mean serum ferritin levels in thalassemia major patients after giving deferasirox and deferoxamine. Annals ASH & KMDC 2017;22:243-48.

(ASH & KMDC 22(4):243;2017)

Introduction

Thalassaemia is a genetic disease characterised by the inability of the body to produce an adequate amount of haemoglobin in red blood cells. The probability for a child to have thalassaemia major is 25% in conditions where both the parents are carrier of the disease. The treatment of this condition is a huge economical and psychological burden on both the family and the government[1].

Thalassaemia is perhaps the most common genetic disorder in Pakistan with over 100,000 thalassaemia patients and about eight million carri-

[1-6] Department of Paediatrics Unit III,
Dow University of Health Sciences, Civil Hospital Karachi

Correspondence: Dr. Amber Kamran
Department of Paediatrics
Email:dramberkamran@hotmail.com
Date of Submission: 24th July 2017
Date of Acceptance: 4th December 2017

ers and life expectancy can be as low as 15 to 20 years[1]. The number of children suffering from thalassaemia major in Pakistan is approximately 40,000 and about 5000 are added each year, which shows that the disease burden is really high in this part of the world[2,3].

A large number of complications in thalassaemia major are mainly due to iron overload as a result of frequent blood transfusions. Extra iron gets accumulated in different tissues and organs of the body especially in the heart, liver and endocrine cells[4]. This chronic iron overload in thalassaemia patients leads to multiple organ failure and is a major cause of death if chelation therapy is not provided appropriately to these patients[5,6]. Within a few years of regular blood transfusion initiation in children with thalassaemia, serum ferritin levels and liver iron concentration (LIC) levels increase, and therefore, require chelation. Studies have shown that when iron chelation therapy is given in an adequate dose, it reduces iron-related complications and improves quality of life and overall survival[7]. Deferoxamine is an iron chelator and binds with iron tightly to form iron-deferoxamine complex which is excreted in both urine and stool. The standard dose used for removing this extra iron is by subcutaneous infusion over 8-12 hours in 5 to 7 days each week because of the short half-life in plasma[8]. Another drug used is deferasirox, which represents a comparatively new class of iron chelators. Since the half-life of deferasirox is up to 16 hours, therefore once daily dose is acceptable to maintain an effective plasma level of the drug[9]. In a group of thalassaemia patients mean change in serum ferritin level in deferoxamine group was (337 ± 0)[10] which units, another study of deferasirox showed mean change in serum ferritin level (235 ± 44.39)[11] which units.

Deferasirox, due to its oral route and once daily dosing, is pain-free, less time-consuming and more cost-effective properties, will be more feasible for the patients to take, as compared to deferoxamine. Literature also shows preference for deferasirox due to its longer half-life[12]. Since there is limited comparative data available in Southeast Asia and due to difference in prevalence of thalassaemia major in eastern and western population, we want to see the comparative effect of deferasirox and deferoxamine on serum ferritin level.

Patients and Methods

The study was conducted at paediatrics department, Civil Hospital, Karachi. The duration of the study was six months from 29th January 2014 to 28th July 2014. It was a randomised clinical trial. A total of 160 thalassaemia patients were included in the study; 80 patients in each group. This sample size was calculated using OpenEpi software, taking mean change in serum ferritin level in deferoxamine group (337 ± 0)[10] and (235 ± 44.39)[11] for deferasirox group. By taking above statistics, CI= 95% and power of study is 80%, and then at least 160 sample size required. Non-probability consecutive sampling technique was used for this study.

The inclusion criteria were; patients diagnosed with thalassaemia major of ages between 1-14 years, of either sex and receiving blood transfusion (atleast once a month) with serum ferritin >1000mcg/L. The exclusion criteria were; patients having anaemia other than thalassaemia, patients who were already using any iron chelating agents and patients who had any sensitivity or allergy to either deferasirox or deferoxamine and thalassaemic children with complications.

The data collection was started after an approval from the institutional ethical committee. The patients were recruited through department of paediatrics, Civil Hospital, Karachi. A total of 160 patients, after fulfilling the inclusion criteria were included in the study. After explaining the purpose and procedure of the study, a written and oral informed consent was taken from guardians of the patients. Each enrolled patient was randomly allocated by lottery method to either group A or group B. Group A received deferoxamine, while deferasirox was given to group B. Pre-treatment and post-treatment ferritin profile was done in both the groups to

assess the iron status in the body. Blood tests were also done for haemoglobin. All the data were entered into a prescribed pro forma. Confounding variables as well as bias was controlled by strictly following the inclusion and exclusion criteria.

The data was entered and analysed with SPSS 19. The quantitative variables like age, weight, height, and serum ferritin at baseline and after 6 months were expressed as mean ± standard deviations, whereas the frequency and percentages were calculated for qualitative variables i.e. gender. T-test was applied to compare mean change of serum ferritin in both groups. The p-value of less than or equal to 0.05 was considered as statistically significant. Confounders were controlled through stratification of age, gender, weight, height, and duration of blood transfusion received to see the impact of these on outcome variables using t-test taking $p \leq 0.05$ as significant.

Results

The results showed that overall there were 96 male and 64 female patients. The mean age of study subjects was 7.54 ± 4.21 years. The mean weight was 19.22 ± 6.84 kg. The mean height was 105.11 ± 20.35 cm. Mean duration of transfusion was 7.81 ± 3.78 months.

Age, weight, height, and duration of transfusion was stratified into two groups. The results showed that 89 patients were ≤7 years and 71 were >7 years of age. 80 patients weighed ≤19 kg and 80 weighed >19 kg. 76 patients were ≤105 cm in height and 84 were >105 cm. 81 patients had undergone ≤7 years of transfusion and 79 had undergone >7 years of transfusion.

The frequency of patients with respect to gender and stratified groups of age, weight, height, and duration of transfusion was also calculated according to two treatment groups.

The serum ferritin levelsbefore and after treatment were observed according to two treatment groups. In the deferasirox group, before treatment mean serum ferritin level was 1385.73 ± 117.01 ng/ml. The minimum level was 1129 ng/ml and the maximum level was 1574 ng/ml. After treatment mean serum ferritin level was reduced to 1047.59 ± 117.08 ng/ml. The minimum level was 789 ng/ml and the maximum level was 1234 ng/ml. In the deferoxamine group, before treatment mean serum ferritin level was 1362.58 ± 134.42 ng/ml. The minimum level was 1133 ng/ml and the maximum level was 1609 ng/ml. After treatment mean serum ferritin level was reduced to 1124.36 ± 134.52 ng/ml. The minimum level was 894 ng/ml and the maximum level was 1370 ng/ml.

Post-treatment the significance of serum ferritin level was observed through t-test. The results showed that post treatment the serum ferritin level between two groups is significantly different with $p<0.01$.

The detailed results for comparisons of mean change of serum ferritin level among the deferasirox and deferoxamine groups are presented in Table 1 and Table 2.

Discussion

Thalassaemia is recognised as the most prevalent genetic blood disorder in Pakistan[1]. However, β thalassaemia, is the most common autosomal single-gene disorder worldwide, and is found in more than 60 countries, with a carrier population of up to 150 million[13,14].

Iron overload is an unavoidable complication suffered by thalassaemia major patients as a consequence of multiple blood transfusions. It is so common that it has been referred to as a "second disease" during treatment of the first[15,16]. Serum ferritin is an easy and inexpensive indirect measurement of iron burden, however, a single measure may not provide a reliable indication of iron levels. The new non-invasive methods of measurement iron storage in the body such as magnetic resonance imaging (MRI) or superconducting quantum interference device (SQUID) have greater sensitivity, but they have limited use in developing countries such as Pakistan because of cost and complexity.

Table 1. Mean difference of serum ferritin level (ng/ml) pre- and post-treatment indeferasirox group.
*T= T value
df= frequency of distribution

		Paired Difference Mean	SD	T	d f	p-value
Gender	Male (n= 54)	338.074	1.330	1868.393	53	0.001
	Female (n= 26)	338.269	1.079	1598.299	25	0.001
Age Groups	≤ 7 (n= 52)	338.173	1.294	1884.036	51	0.001
(years)	>7 (n= 28)	338.071	1.184	1510.760	27	0.001
Weight	≤ 19 (n= 52)	338.115	1.263	1931.016	51	0.001
Groups (kg)	>19 (n= 28)	338.179	1.249	1432.994	27	0.001
Height Groups	≤ 105 (n= 50)	338.120	1.256	1903.796	49	0.001
(cm)	>105 (n= 30)	338.167	1.262	1468.000	29	0.001
Duration of transfusion	≤ 7 (n= 47)	338.000	1.234	1878.432	46	0.001
(months)	>7 (n= 33)	338.333	1.267	1534.536	32	0.001

Table 2. Mean difference of serum ferritin level (ng/ml) pre- and post-treatment in deferoxamine group

		Paired Difference Mean	SD	T	d f	p-value
Gender	Male (n= 42)	238.333	0.928	1663.830	41	0.001
	Female (n= 38)	238.079	0.941	1559.627	37	0.001
Age Groups	≤ 7 (n= 37)	238.162	0.958	1512.482	36	0.001
(years)	>7 (n= 43)	238.256	0.928	1683.185	42	0.001
Weight	≤19 (n= 28)	238.357	0.911	1383.848	27	0.001
Groups (kg)	>19 (n= 52)	238.135	0.950	1807.000	51	0.001
Height	≤105 (n= 26)	238.308	0.884	1374.515	25	0.001
Groups (cm)	>105 (n= 54)	238.167	0.966	1801.978	53	0.001
Duration of transfusion	≤ 7 (n= 34)	238.206	1.008	1377.354	33	0.001
(months)	>7 (n= 46)	238.217	0.892	1810.752	45	0.001

Table 3. Comparison of post-treatment mean difference of serum ferritin level (ng/ml) amongdeferasirox and deferoxamine groups

	Mean	SD	p-value
Deferasirox	1047.59	111.08	0.001
Deferoxamine	1124.36	134.52	

Independent sample t-test was applied.
p-value ≤ 0.05 considered as significa

The importance of chelation therapy can be appreciated from the fact that levels of ferritin are inversely linked to the survival in thalassaemia major patients[15]. To sustain children affected with β - thalassaemia, monthly blood transfusions accompanied by iron chelation therapy is needed, and requirements for treating one annual birth cohort for one year are 90,000 units of blood plus 22 million dollars' worth of deferoxamine[14,17]. Many studies concluded that cirrhosis of liver is associated with increase in serum ferritin level[16-21].

A study conducted in Islamabad, showed that the mean serum ferritin level in patients with beta thalassaemia was 3390 ng/ml[21]. As excessive iron can lead to organ damage, chelation therapy is employed to lower its levels[15]. Borgna-Pignatti et al. reported that a lower ferritin concentration predicted longer survival, and reduced risk of various complications[16]. The importance of chelation therapy can be appreciated from the fact that levels of ferritin are inversely linked to the survival in thalassaemia major patients[15].

Iron chelation therapy is a lifelong requirement for transfusion dependent patients with β-

thalassaemia, but to date, long-term efficacy and safety data from prospective clinical trials in paediatric and adult patients are limited[22].

In a study[15], 79 cases of beta thalassaemia major were analysed. Among them, 46 (58.2%) were male while 33 (41.8%) were females. The mean age was 10.8 ± 4.5 years. The mean serum ferritin level was 4236.5 ng/ml, which is markedly higher than normal (12-122 ng/ml)[15,23]. As expected, serum ferritin values were much lower (3319.6 ± 1925.8 ng/ml) in the group who received chelation therapy as compared to those who did not use the medication (5514.8 ± 2383.0 ng/ml)[15].

In another study, results confirmed the efficacy of deferasirox in reducing serum ferritin level in a patients with β -thalassaemia major from base line 2836 ± 456 ng/ml to 2000 ± 535.1 ng/ml after one year of therapy (serum ferritin from base line -835ng/ml with p-value<0.001). This gives information to monitor ferritin levels every 3-6 months. Our results became significant statistically only after 6 months of therapy which is explained by redistribution of iron between reticuloendothelial system and hepatic iron in first 3-6 months of therapy making no significant statistical change. The reduction of serum ferritin in present study is higher than the result done by Capellini.

Another prospective study reported long-term monitoring of the efficacy and safety of iron chelation with deferasirox in both paediatric and adult patients with thalassaemia. It also represents the first report of observed long-term effects on paediatric growth and adolescent sexual development for any oral iron chelation therapy. Overall, two-thirds of patients completed the 5-year study[22].

Growth of paediatric patients and sexual development of adolescent patients with β -thalassaemia is of particular relevance, because multiple factors, including iron toxicity, can lead to reduced stature and delayed puberty in this population. Although the prevalence has decreased since iron chelation therapy has become available, many patients continue to experience complications of growth and sexual development, which are often associated with poor compliance to deferoxamine[22].

Deferasirox did not show an adverse effect on paediatric growth or adolescent sexual development in paediatric patients, who are prone to growth retardation as a result of iron overload. Appropriate dose adjustments led to clinically relevant decreases in LIC and serum ferritin, highlighting the necessity for dose titration to achieve negative iron balance. Deferasirox, with dosing tailored to individual patient requirements, is therefore an effective long-term treatment for transfusional iron overload in patients with β -thalassaemia[22].

In our study, more patients were male and the mean age of study subjects was 7.54 ± 4.21 years. In the deferasirox group, before treatment mean serum ferritin level was 1385.73 ± 117.01 ng/ml and it was reduced to 1047.59 ± 117.08 ng/ml. In the deferoxamine group, before treatment mean serum ferritin level was 1362.58 ± 134.42 ng/ml and after treatment this was reduced to 1124.36 ± 134.52 ng/ml. The reduction in serum ferritin level is significant, which proves that deferasirox is more effective than deferoxamine in both male and female patients of age 1-14 years.

The main limitations of the present study include a single centre experience, low female representation in the study cohort and a non-randomised study design, small sample size and urban environment therefore, the results might not be generalised to larger populations.

Conclusion

Deferasirox is effective, safe and tolerable chelation therapy in treatment of β-thalassaemia major with iron overload due to its ability to provide constant chelation coverage and potential to improve compliance due to its easy administration.

References

1. Shaikh Z. Thalassemia: Pakistan's Fight to Eradicate this Condition [Online]. Global Health & Development 2011. Available from:http://aglobalvillage.org/journal/issue3/global_health_and_development/thalassemia/. Accessed on October 31, 2017.
2. Ahmad S, Saleem M, Modell B, Petrou M. Screening extended families for genetic hemoglobin disorders in Pakistan. N Engl J Med 2002;347;1162-8. [DOI: 10.1056/NEJMsa013234].

3. Hafeez M, Aslam M, Ali A, Rashid Y, Jafri H. Regional and ethnic distribution of beta thalassemia mutations and effect of consanguinity in patients referred for prenatal diagnosis. J Coll Physicians Surg Pak 2007;17:144-7. [DOI: 03.2007/JCPSP.144147].

4. Britton RS, Leicester KL, Bacon BR. Iron toxicity and chelation therapy. Int J Hematol 2002;76:219-28.

5. Schrier SL, Angelucci E. New strategies in the treatment of the thalassemias. Annu Rev Med 2005;56:157-71. [DOI: 10.1146/annurev.med.56.082103.104718].

6. Rund D, Rachmilewitz E. Beta-thalassemia. N Engl J Med 2005;353:1135-46. [DOI: 10.1056/NEJMra050436].

7. Olivieri NF, Brittenham GM. Iron-chelating therapy and the treatment of thalassemia. Blood1997;89:739-61.

8. Brittenham GM, Griffith PM, Nienhuis AW, McLaren CE, Young NS, Tucker EE, et al. Efficacy of deferoxamine in preventing complications of iron overload in patients with thalassemia major. N Engl J Med 1994;331:567-73. [DOI: 10.1056/NEJM199409013310902].

9. Al-Wataify AS. Efficacy and safety of deferasirox therapy on β-thalassemia major patients in Babylon thalassemia centre [Online]. Jena School for Microbial Communication 2013;3:125-30. Available from: http://jlps.univsul.edu.iq/issues/jsmc-vol-3-no-2-2013. Accessed on October 31, 2017.

10. Saleem M, Ahmad PA, Mubarik A, Ahmad SA. Distribution pattern of hemoglobinopathies in northern areas of Pakistan. J Pak Med Assoc 1985;35:106-9.

11. Weatherall DJ, Clegg JB. Inherited haemoglobin disorders: an increasing global health problem. Bull World Health Organ 2001;79:704-12.

12. Riaz H, Riaz T, Khan MU, Aziz S, Ullah F, Rehman A, et al. Serum ferritin levels, socio-demographic factors and desferrioxamine therapy in multi-transfused thalassemia major patients at a government tertiary care hospital of Karachi, Pakistan. BMC Res Notes 2011;4:287. [DOI: 10.1186/1756-0500-4-287].

13. Knovich MA, Storey JA, Coffman LG, Torti SV, Torti FM. Ferritin for the clinician. Blood Rev 2009;23:95-104. [DOI: 10.1016/j.blre.2008.08.001].

14. Cao A, Rosatelli MC, Galanello R. Control of beta-thalassaemia by carrier screening, genetic counselling and prenatal diagnosis: the Sardinian experience. Ciba Found Symp 1996;197:137-51.

15. Waalen J, Felitti VJ, Gelbart T, Beutler E. Screening for hemochromatosis by measuring ferritin levels: a more effective approach. Blood 2008;111:3373-6. [DOI: 10.1182/blood-2007-07-102673].

16. Ikram N, Hassan K, Younas M, Amanat S. Ferritin levels in patients of betathalassaemia major [Online]. Int J Pathol 2004;2:71-4. Available from: http://jpathology.com/wp-content/uploads/2016/03/Ferritin-levels-in-Pts-of-Beta-Thalassaemia-Major1.pdf. Accessed on October 31, 2017.

17. Cappellini MD, Bejaoui M, Agaoglu L, Canatan D, Capra M, Cohen A, et al. Iron chelation with deferasirox in adult and pediatric patients with thalassemia major: efficacy and safety during 5 years' follow-up. Blood 2011;118:884-93. [DOI: 10.1182/blood-2010-11-316646].

18. Hows J, Hussein S, Hoffbrand AV, Wickramasinghe SN. Red cell indices andserum ferritin levels in children. J Clin Pathol 1977;30:181-3.

19. Cappellini MD, Porter J, El-Beshlawy A, Li C, Seymour JF, Elalfy M, et al. Tailoring iron chelation by iron intake and serum ferritin: the prospective EPIC study of deferasirox in 1744 patients with transfusion-dependent anemias. Haematologica2010;95:557-66. [DOI: 10.3324/haematol.2009.014696].

20. De Sanctis V, Eleftheriou A, Malaventura C; Thalassemia International Federation Study Group on Growth and Endocrine Complications in Thalassemia. Prevalence of endocrine complications and short stature in patients with thalassemia major: a multicenter study by the Thalassemia International Federation (TIF). Pediatr Endocrinol Rev2004;2:249-55.

21. Low LC. Growth of children with beta-thalassaemia major. Indian J Pediatr 2005;72:159-64.

22. Roth C, Pekrun A, Bartz M, Jarry H, Eber S, Lakomek M, et al. Short stature and failure of pubertal development in thalassaemia major: evidence for hypothalamic neurosecretory dysfunction of growth hormone secretion and defective pituitary gonadotropin secretion. Eur J Pediatr1997;156:777-83.

23. Najafipour F, Aliasgarzadeh A, Aghamohamadzadeh N, Bahrami A, Mobasri M, Niafar M, et al. A cross-sectional study of metabolic and endocrine complications in beta-thalassaemia major. Ann Saudi Med2008;28:361-6.