International Journal of Health Sciences and Research
www.ijhsr.org ISSN: 2249-9571

Original Research Article

Effect of Oral Chelation Therapy on Physical Growth and Serum Ferritin Levels in Children with Thalassemia Major in Tertiary Care Hospital in Western Maharashtra

Dr. Sangita Kumbhojkar[1], Dr. Rahul Murugkar[2], Dr. Sudhir Sarawade[3]

[1]Associate Professor, [2]Senior Resident, [3]HOD & Professor,
Dept. of Pediatrics, R.C.S.M. Govt. Medical College Kolhapur.

Corresponding Author: Dr. Sangita Kumbhojkar

Received: 26/11/2016 *Revised: 14/12/2016* *Accepted: 19/12/2016*

ABSTRACT

Objectives: To study the effects of oral iron chelation regimen on serum ferritin levels, the physical and sexual growth of children with thalassemia major

Methods:-This is prospective study of total 42 Children of thalassemia major receiving blood transfusion in tertiary care hospital. All the children included in the study were subjected to anthropometry measurement and SMR staging. Routine investigations along with serum ferritin level were estimated 6 monthly. Patients studied in groups 1 receiving no chelation therapy and a group 2 receiving oral chelator .Growth assessment was done by growth Chart.

Results: The one year mean ferritin level after 12 months of enrollments in group 01 was 5567.71 ng/ml and in group 02:4726.25 ng/ml. A statistically significant decline was observed in the 1 year serum Ferritin in group 2.Mean ferritin levels were significantly higher in short stature than in the patients with normal height. Among adolescents (n=12) 10 patients are short statured (66.66%) Amongst short statured patients (n=15). 10 patients (25.64%) were undernourished and 3(7.69%) were severely malnourished. Four adolescent patients (33.3%) in this study had delayed onset of puberty. S. ferritins in patients with delayed puberty were higher compared to those in adolescent patients with normal puberty.

Conclusion: Thalassemia patients are short, have low rate of growth and BMI (Body Mass Index) and have either delayed or absent pubertal spurt, which is correlated with status of iron overload and high serum ferritin. Iron chelating agent like deferasirox have significant role in reduction of serum ferritin.

Key words: Thalassemia major, Chelation therapy, Growth Assessment, Sexual maturity rating(smr) serum ferritin.

INTRODUCTION

Thalassemia is a group of inherited haematological disorders characterised by early onset anaemia resulting from reduced synthesis of one or more globin chains which can be caused by different globin gene mutations. [(1)]

Reportedly, there are about 240 million carriers of beta-thalassemia worldwide, and in India alone, the number is approximately 30 million with a mean prevalence of 3.3%. [(2)] Every year approximately 100,000 children with Thalassemia Major are born world over, of which 10,000 are born in India.

Thalassemia mainly characterised by a reduced ability to produce effective haemoglobin. The mainstay of treatment of Thalassemia is regular blood (Packed Red Blood Cells) transfusions. The major complications of blood transfusion are those related to transmission of infectious agents and development of iron overload. Repeated transfusions result in excessive iron overload in the body, removal of which is achieved through iron Chelation.

Desferrioxamine and Deferiprone are two such chelating agents being used in patients on blood transfusion. When administered in conjunction with blood transfusion regimens, chelation is able to delay the onset of cardiac diseases due to iron overload and in some patients even prevent its occurrence. Defarasirox-ICL670 (EXZADE) belonging to tridentate triazole, with high affinity to iron as Fe+++ and chelates at a ratio of 2:1(Defarasirox:Iron) is a new oral chelator for treatment of iron overload associated with chronic blood transfusion. [(3)]

We did this study with 39 Thalassaemia patients receiving blood transfusion at regular interval to assess physical growth and Sexual Maturity Rating and to study the effect of chelation therapy on Serum Ferritin levels.

Aims and objectives

1. To study the effects of oral Iron chelation regimen on the physical and sexual growth of children aged 1-15 years with Thalassemia Major.
2. To study the efficacy of chelation therapy on serum ferritin level.

MATERIALS AND METHODS

This is an observational prospective study done in CPR Hospital affiliated to RCSM Govt. Medical College, Kolhapur is a tertiary care hospital in western Maharashtra included 42 children aged 1 to 15 years with confirmed diagnosis of Thalassemia major receiving regular blood transfusions at CPR Hospital during December 2011 to December 2012. Approval of Institutional Ethical Committee was obtained prior to study.

All details were recorded in a pre-decided pro-forma which included personal information, detailed history, thorough clinical examination, routine investigations and anthropometric evaluation of all patients and occurrence of side effects of therapy if at all. Anthropometric parameter like Weight was taken on a digital weighing scale. Height was measured by Stadiometer with patients made to stand upright with heel, buttocks, shoulder blade and occiput touching the wall and Frankfurt plane parallel to floor. Body Mass Index (BMI) was determined using weight and height. Physical examination of all systems was done thoroughly. Assessment of sexual maturity rating (SMR) was done in all children 10 years or older. Delayed puberty was defined by non-appearance of breast buds or pubic hair by 14 years of age in girls and no increase in testicular volume greater than 4ml and pubic hair by 15 years in boys. In addition to clinical data, screening for hepatitis B, hepatitis C, HIV was done. Serum Ferritin levels were estimated 6 monthly by chemiluminescence method on ADVIA CENTAUR CP system. Comparision done between Baseline ferritin (At start of study) and at 1 year ferritin level.

The patients were studied in 2 groups-

Group 1: This group included 15 Children receiving ‘no’ Chelation therapy.

Group 2: This group included 24 Children receiving ‘oral’ Deferasirox by 30 mg / kg / day in once daily or Deferiprone by 75 mg / kg / day in three divided doses daily.

Duration of chelation therapy was recorded in months or years along with regular blood transfusion 3 to 4 weekly.

Expected and percentile for weight for age, height for age and Body Mass Index (BMI) for age were noted from CDC 2000 charts and used for various comparisons and statistical tests. WHO Z score charts used for z score. Weight for age z score chart available up to 10 yr .Z score weight for age comparison done up to 10 yr.

Statistical analysis

Data analysis done by using SPSS (Statistical package for social sciences) version 17.0. We have used 2 independent sample t-test, paired t-test, Pearson correlation coefficient to find the significance of ferritin level in patients on chelation therapy and not on chelation therapy at baseline as well as in follow up.
P-value < 0.05 considered as significant.

RESULTS

Out of 42 thalassemia patients, 3 patients lost follow up. Among 39 patients, 17 (43.5%) were female and 22 (56.5%) were male. Patients were 1 years to 15 years of age with mean age of 7.21 years. The mean age in group 1(Not on Iron chelator) was 6.83 years, in group 2 (on iron chelator)-7.6 years. (Table 1)

Table 1: Mean age of patients among the two groups

Group	No. of Patients.	Mean Age in years
Not on Chelator	15	6.83
Oral Chelator	24	7.6
Total	**39**	**7.21**

Twenty seven (69.23%) patients were between 2 years to 9 years and twelve (30.76%) were adolescents between 10 years to 15 years.

The remaining 38.5% patients (group 1) were not taking chelation therapy either due to low socioeconomic status or non availability of drugs. The minimum serum ferritin level was 1438ng/ml in a 2 years old male in group 2 and maximum of 11000 ng/ml in a 15 years old male in group 2. The 1 year Mean Ferritin level, approximately after 12 months of enrolment, in group 1 was 5567.71 ng/ml, in group 2-4726.25 ng/ml respectively. In our study, the mean duration of chelation therapy was 1.19 years in group 2 (oral chelation).

A statistically significant decline ($p<0.001$)was observed in the one year serum Ferritin levels (approximately at one year interval from enrolment) in group2 patient (Table2). Statistically significant increase observed in patient not on chelator.

Table 2: The Baseline and 1 yr mean Ferritin levels among the groups: Group 1 Table (a), Group 2 table (b)

Table 2(a)

		N	Mean	SD	
Group 1 (Not on chelator)	Baseline_Feritin_level	15	4931.27	1884.68	p<0.001
	1 yr_Feritin_level	15	5470.53	1902.92	

Test used paired t-test
Results significant increment in ferritin level at 1 year

Table 2(b)

Paired Samples Statistics					
		N	Mean	SD	p-value
Group 2 (on oral chelator)	Baseline_Feritin_level	24	5213.00	2521.19	< 0.001
	1 yr_Feritin_level	24	4726.25	2349.13	

Test used paired t-test
Results significant fall in ferritin level at 1 year

Table 3: Observed and standard mean weight, height and BMI in group 1 (non chelator) :(15 patients)

Variables	Mean	SD	p-value
Observed Weight	14.35	1.06	0.001*
Standard Weight	16.23	1.25	
Observed Height	114.2	14.42	0.054
Standard Height	125.67	16.77	
Observed BMI	18.93	4.68	0.015*
Standard BMI	26.76	10.28	

* Significant, 2 Independent sample t test

Table 4: Observed and standard mean weight, height and BMI in group 2 patients :(on chelation) (24 patients)

Variables	Mean	SD	p-value
Observed Weight	22.54	7.32	0.026*
Standard Weight	29.89	13.94	
Observed Height	119.92	17.98	0.139
Standard Height	128.98	23.39	
Observed BMI	15.16	1.49	0.002*
Standard BMI	16.67	1.72	

* Significant, 2 Independent sample t test

Observed weight and height of each patient was compared to CDC 2000 growth charts as WHO weight charts are available up to 10 yrs. The growth curves of patients for all parameters ran below Indian Growth Standards among all the groups. Significant difference existed in the mean values of various parameters of patients and Indian standards: weight and BMI in group 1and in group 2 (Table3, 4)

The Z score for weight for age was applied to children less than 10 years. According to weight for age Z score, 14

(18.5%) patients were underweight (weight for age less than -2 SD). There was no significant association between weight for age Z scores in children less than 10 years among the groups.

Fifteen (38.46%) patients had short stature (height for age less than-2 SD). A statistical significance was not observed between Height for age Z score and patients of the groups.

The mean serum Ferritin levels were higher in short statured patients (height for age Z scoreless than-2SD) in group 1 (40%) as compared to group 2 (37.5%) (Table 5)

Table 5: Height for age Z scoreless than – 2SD and less than-3SD in the groups

Groups	< -2 SD	< - 3SD	Mean Ferritin level (ng/ml)
1 (15)	6 (40%)	2 (13.33%)	5200.9
2 (24)	9 (37.5%)	1 (4%)	4969.25

10 patients (25.64%) were undernourished and 3 (7.69%) were severely malnourished having BMI for age Z scores < -2SD and < - 3SD respectively.

Table 6:- BMI for age Z scores in the two groups:

BMI (z-score)		Group		Total
		Not on Chelator	Oral @	
< -3 SD	N	1	2	3
	%	6.67%	8.3%	7.69%
< -2 SD	N	4	6	10
	%	26.67%	25%	25.62%
< -1 SD	N	3	1	4
	%	20%	4.1%	10.25%
<Median	N	6	12	18
	%	40%	50%	46.15%
<1 SD	N	1	3	4
	%	6.4%	12.5%	10.25%
Total	N	15	24	39
	%	100.0%	100.0%	100.0%

P-value 0.263 test used Chi-square test (By Yate's correction)

In our study, 12 children were aged between 10.1 years to 18 years. Group 1 and 2 had 4 and 8 adolescents respectively (Table 14). In adolescent patients 4 children (33.3%) in this study had delayed onset of puberty/ pubertal spurt. Three girls were above 14 years and 1 boy was above 15 years of age.

The mean Ferritin levels in group1 and 2 were observed to be higher in patients with delayed puberty. However, this association was not statistically significant (Table 7).

Table 7: The 1 year mean Ferritin levels among adolescents group 1 and 2:

Group	Adolescent	No.	Mean	SD
1 year Mean Ferritin level (ng/ml) in group1	Delayed	1	8300	
	Normal	3	7820	800.75
1 year Mean Ferritin level (ng/ml) in group 2	Delayed	3	8726.66	1294.96
	Normal	5	6496	935.67

2 independent sample t-tests

There is statistically significant difference between mean ferritin levels of Thalassemia Children and Adolescent with Ferritin level 3915.20ng/ml (SD 1418.10) and 7631.8 ng/ml (1328.72) respectively. (p-value:<0.001) (table 8)

Table 8: Comparison of mean ferritin level of Thalassemia children and adolescent

	N	Mean sr. ferritin level	SD
Thallassemia children (1-9)	27	3915.20	1418.10
Adolescent	12	7631.8	1328.72
p-value:<0.001			
Two in dependant sample t-test			

Mean ferritin level higher among short stature (<-2 SD) as compared to normal (>-2 SD) seen in group 1 and 2. Statistically significant higher level seen in group 2 in short stature ferritin level 7127.66 (SD 1911) and in normal stature 3624.8 (SD 1680.9) with p-value: 0.001. (Table 9)

Table 9: comparision mean ferritin level of study to height among groups.

Group	Height	No	Mean	SD	p- value
Mean ferritin level in group 1	Short stature (<-2 SD)	6	6089	2120	0.148
	Normal (>-2 SD)	9	4608	1569.97	
Mean ferritin level in group 2	Short stature (<-2 SD)	9	7127.66	1911	0.001
	Normal (>-2 SD)	15	3674.8	1680.9	

DISCUSSION

Physical growth is affected in a large number of patients with transfusion dependent thalassemia. A study of patients aged 10-27 years with thalassemia major found short stature in 70% male and 73% of female. [(4)] Another study found short stature in 29.7% of patients. [(5)]

The etiological factors leading to growth retardation in transfusion dependent thalassemia are varied, with iron load induced endocrinopathies, chronic anaemia, folate and zinc deficiencies, having been implicated in this complication. The increasing mean survival age of thalassemia patient is indicative of the fact that modern therapies are generally safe and effective but it is becoming increasingly clear that as thalassemia patients approach the age of puberty, many develop growth retardation and pubertal failure and many other endocrine complications like hypogonadism, hypothyroidism and diabetes mellitus. Growth deficiency and short stature is commonly seen especially in adolescence.

Our study comprised 39 patients, 15 (38.46%) patients in group 1 were not on chelation therapy. Their mean serum ferritin level on enrolment was 4931.27ng/ml. Their age ranged between 2 year to 13 years (mean age 6.83 year). Subsequently mean sr ferritin level approximately after 12 months was found to be 5470.53ng/ml which is increased. (Statistically significant) (Table 2)

Group 2 had 24 (61.5%) patients who were on oral chelation therapy (mean duration 1.19 years) of which 4 were on Deferiprone and 20 on deferasirox. Their age ranged from 2 years to 15 years (mean age 7.6 years). The mean serum ferritin level on enrollment was 5213 ng/ml and approximately after 12 months was 4726.25 ng/ml which is decreased. (Statistically significant). (Table 2b)

The mean levels of ferritin depend on several factors, including age at presentation, age of beginning regular Packed Red Blood Cell transfusion, age at starting iron chelation therapy, efficacy of the iron chelating drug and its compliance and the age group of the reported series of patients.

In our study, 15 (38.46%) patients had short stature (height for age Z scoreless than-2SD). In group 1, six patient (40%) had height less than <- 2 SD with mean ferritin level 5200ng/ml. In group 2, nine Patient (37.5%) had height less than <-2 SD with mean ferritin level 4969.25ng/ml. highlighted in (table 5). Group 1 had higher ferritin level more short stature patients as compare to group 2 but statistically not significant due inadequate sample size and short study period. Studies have noted similar finding. [(6)]

Harish K Pemde et al (2011) studied 154 patients with mean age 9.19 years (range 0.5-20 years).One-third (33.11%) of the patients had short stature, 13% were thin, and 10.82% were very thin (BMI *z*-score,-3SD). Height *z*-scores had significant correlation with mean ferritin levels, Mean ferritin levels were significantly higher in patients with short stature than in the patients with normal height. One-fifth (19.40%) of adolescent patients had delayed puberty. [(7)]

Kumar P et al (2010) studied the effect of chelation therapy in three groups. height of 56% of patients and the weight of 49% of patients was below 3rdcentile for their age and sex when compared with CDC-2000 standard, indicating profound growth retardation among thalassemics. [(8)]

Height reduction is more with increasing age in thalassemia children. In our study, among Adolescents (n=12) 10 patients are short stature which constitute 66.66% of total short stature patients (n=15). Our finding correlated well with the finding of the other studies. [(9,10)]

In the present study Overall Z score for height for age and weight for age were low. Ten patients (25.64%) were undernourished and 3 (7.69%) were severely malnourished, having BMI for age Z score less than 2SD below mean for normal standards (Table 9). As most of patients belong to low socioeconomic background and non availability of iron chelating drugs leading to growth faltering is one of major cause found in our study. Similar results also seen in study done by Anita Saxena (2003) concluded that thalassemia patients are short, have low rate of growth and BMI and have either delayed

or absent pubertal spurt, which is related to low hemoglobin and high ferritin levels and sub-optimal iron chelation therapy. Poor socioeconomic background compounds the problem. [(11)]

The pathogenesis of late impairment of growth and sexual maturation in transfused thalassemia patients is not yet well classified. It is generally believed that it is directly related to iron toxicity, especially of the endocrine glands. The pubertal growth spurt is often absent or delayed and even patients with normal growth spurt can have delayed sexual maturation.

Out study included 12 adolescent patients (4 in group1 and 8 in group 2). Among these four patients (33.3%); 3 girls and 1 boy were above the age of 14 and 15 years respectively, had obvious delayed puberty diagnosed clinically by SMR staging.

A varied proportion of patients with delayed puberty or hypogonadism have been reported in the other studies. [(12)]

Gonadal failure is related to age at which chelation therapy is started. Patients with high serum ferritin levels more commonly experience gonadal failure. However, serum ferritin levels in our patients with delayed puberty were higher compare to those in adolescent patients with normal puberty. Statistically not significant due inadequate sample size. (Table 7)

In our study, statistically significant higher serum ferritin level seen in Thalassemia children and adolescents Adolescent with Ferritin level 3915.20ng/ml (SD 1418.10) and 7631.8 ng/ml (SD 1328.72) respectively (table 8) Similar result seen in study done by Singhal et al. [(13)]

In present study statistically significant difference seen in mean ferritin level during study period and height <-2 SD in group 2 (Table9). In short stature ferritin level 7127.66 (SD 1911) and in normal stature 3624.8 (SD 1680.9) with p-value: 0.001. Similar finding seen in study done by A Hamidah et al. [(14)]

A statistically significant decline was observed in the 1 year serum Ferritin levels (approximately at one year interval from enrolment) in group 2 patients, results were seen with Serum ferritin decline from 5213 ng/ml (=µg/L) to 4726.25 ng/ml ($p<0.01$) suggesting oral chelation therapy was beneficial (Table 2b). Chandra et al studied 40 patients of Beta thalassemia with Deferasirox in Indian children serum ferritin levels fell in 24 of 34 patients (75%) who received deferasirox for 1 yr from mean (SD) 6323.37 (2756.5)µg /L to 5458.91 (2301.2) µg /L ($p<0.05$). [(15)]

CONCLUSION

Thalassemia patients are short, have low rate of growth and BMI; and have either delayed or absent pubertal spurt, which is correlated with status of iron overload and high serum ferritin. Iron chelating agent like deferasirox have significant role in reduction of serum ferritin levels.

REFERENCES

1. Louis C.K. Low. Growth of children with beta thalassemia major. Indian J Pediatr 2005 Feb; 72:159- 160.
2. Verma IC, Choudhry VP, Jain PK. Prevention of thalassemia: A necessity in India. Indian J Pediatr 1992; 59: 649-654.
3. Lokeshwar MR, Shah N, Kanakia S, Mangalani M. Thalassemia. In: Parthasarathy A, editor. IAP Textbook of Pediatrics. 4th ed. New Delhi: Jaypee; 2009. p. 794-815.
4. Najafipour F, Aliasgarzadeh A, Aghamohamedzadeh N, Bahrami A, Mobasri M, Niafar M,et al. A cross sectional study of metabolic and endocrine complications in beta thalassemia major. Ann Saudi Med. 2008; 28: 361-366.
5. Li CK, Luk CW, Ling SC, Chik KW, Yuen HL, Li CK et al. Morbidity and Mortality patterns of thalassemia major patients in Hong Kong: retrorespective study. Hong Kong Med. J. 2002; 8: 255-260.
6. Shalitin S, Carmi D, Weintrob N, Phillip M, Miskin H. Serum ferritin

level as a predictor of impaired growth and puberty in thalassemia major patients. Eur J Haematol 2005 Feb; 74(2):93-100.

7. Pemde HK, Chandra J, Gupta D, Singh V, Sharma R, Dutta AK. Physical growth in children with transfusion-dependent thalassemia. Pediatric Health, Medicine and Therapeutics 2011; 2:13-19.
8. Kumar P, Ghalaut V S, Abrol P, Sen J, Sachdeva A. Effect of different modalities of chelation in beta Thalassemia. Journal of Clinical and Diagnostic Research. 2010 August; (4): 2728-2732.
9. Shalitin S, Carmi D, Weintrob N, Phillip M, Miskin H. Serum ferritin level as a predictor of impaired growth and puberty in thalassemia major patients. Eur J Haematol 2005 Feb; 74(2):93-100.
10. Karamifar H, Shahriari M, Amirhakimi GH. Linear Growth Deficiency in Beta-Thalassemia Patients: Is It Growth Hormone Dependent? IJMS 2002 june; 27(2): 47-50.
11. Saxena A. Growth Retardation in Thalassemia Major Patients. Int J Hum Genet 2003; 3(4): 237-246.
12. Shamshirsaz AA, Bekheirnia MR, Kamgar M, Pourzahedgilani N, Bouzari N, Habibzadeh M, et al. Metabolic and endocrinologic complications in beta thalassemia major: A multicentric study inTehran. BMC Endocr Disord 2003; 3: 4-9.
13. Singhal B, Shama N, Mathur R. IRON OVERLOAD AND GROWTH OF THALASSEMIC PATIENTS IN MARWAR REGION Int Jr Pharmaceutical Sciences and Reaserch 2012; 3(7): 2043-2049.
14. Hamidah A, Arini MI, Zarina AL, Zulkifli SZ , Jamal R. Growthvelocity in transfusion depedent prepubertal Thalassemia patients. Southeast Asian J Trop Med Public Health. 2008 September; 39(5):900-905.
15. Chandra J, Chaudhary H, Pemde H, Singh V, Dutta AK. Safety and efficacy of deferasirox in multitransfused Indian children with β-thalassaemia major. Ann Trop Paediatr. 2011; 31(1):47-51.

How to cite this article: Kumbhojkar S, Murugkar R, Sarawade S. Effect of oral chelation therapy on physical growth and serum ferritin levels in children with thalassemia major in tertiary care hospital in western Maharashtra. Int J Health Sci Res. 2017; 7(1):45-51.

****

International Journal of Health Sciences & Research (IJHSR)

Publish your work in this journal

The International Journal of Health Sciences & Research is a multidisciplinary indexed open access double-blind peer-reviewed international journal that publishes original research articles from all areas of health sciences and allied branches. This monthly journal is characterised by rapid publication of reviews, original research and case reports across all the fields of health sciences. The details of journal are available on its official website (www.ijhsr.org).

Submit your manuscript by email: editor.ijhsr@gmail.com OR editor.ijhsr@yahoo.com