Physical Growth in Children with Transfusion Dependent Thalassemia

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Abstract

Background: Thalassaemia is a major congenital hemato-logical disease of Bangladesh. Poor growth and delayed maturation occurs in these patients commonly. This study was aimed to evaluate the physical growth in Transfusion Dependent Thalassemia (TDT).

Materials and methods: This cross-sectional comparative study enrolled 60 diagnosed Children with Transfusion dependent Thalassemia over I year and carried out in Pediatric Hematology and Oncology unit and Hematology Department of Chittagong Medical College Hospital, Chattogram. Among them, 30 children received blood transfusion >12 times per year was considered as group I and rest 30 children received blood transfusion ≤12 times per year was considered as group II. Statistical analysis was done by using window based computer software devised with Statistical Packages for Social Sciences (SPSS-22).

Results: The mean serum ferritin was higher in group I than group II(1243.77±761.626 and 293.77±142.686 respectively). Almost two third (60.0%) patients were severely stunted in group I and 8(26.7%) in group II. 28(93.3%) patients had under weight (<-2SD) in group I and 18(60.0%) in group II. The difference were statistically significant between two groups.

Conclusion: Growth retardation (Height for age) was significant with higher number of blood transfusion and higher serum ferritin level .

Key words: Growth; Serum ferritin; Transfusion dependent thalassemia.

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Introduction

It is estimated that 7000 new babies born with thalassemia each year in Bangaladesh.[1] The thalassemias are inherited disorders of hemoglobin (Hb) synthesis. β thalassemia occurs when there is a quantitative reduction of globin chains that are usually structurally normal.[2] Anemia in β thalassemia thus results from a combination of ineffective erythropoiesis, peripheral hemolysis and an overall reduction in hemoglobin synthesis. Their clinical severity widely varies, ranging from asymptomatic forms to severe or even fatal entities.

Thalassemia, depending on its severity, the disease may cause an enlarged spleen, bone weakness and growth problems and may require transfusions starting in early childhood. The blood transfusions lead to the most serious complications. Children with this Illness usually end up also suffering from other complications such as heart disease, cirrhosis of the liver, diabetes, facial deformities and spinal cord abnormalities.[3] The complications of thalassemia like growth retardation, fractures, heart diseases etc occurs in their early lives which cannot be prevented and it affects the child's daily activities. There is a lack of knowledge and awareness among parents and care givers about the onset of disorders of thalassemia and its life threatening complications which makes the children to lead a miserable life.

Abnormal growth resulting in stunting and delayed or absent puberty is characteristic of children with thalassaemia major.[4] One-third (33.11%) of the patients had short stature in thalassemia.[5]

Iron is deposited in the different organs of the body in thalassemia patients due to regular blood transfusion of these patients.[6] Iron overload remain the main causes of poor growth.[7] Regular blood transfusions can maintain pre -transfusion Hb levels, but if serum ferritin levels are higher than the desired levels, patients physical growth can be affected.[5] Physical growth is hampered due to excess iron deposition in regulatory organ like

endocrine gland. Therefore, along with maintaining Hb levels, it is important to have effective iron chelation therapy to minimize retardation of growth in patients with transfusion-dependent thalassemia. There are large number of young patients with transfusion dependent thalassemia but few studies on Physical Growth in Children with Transfusion Dependent Thalassemia in Bangladesh. So this study was aimed to assess the physical growth pattern among the transfusion dependent thalassemia patients and determine the relationship between serum ferritin with growth status.

Materials and methods

A cross sectional comparative study was conducted on TDT patients from 1st January 2015 to 31st December 2015 in Pediatric Hematology and Oncology unit and Department of Hematology in Chittagong Medical College Hospital (CMCH) Chattogram. The Patients diagnosed as thalassemia by serum electrophoresis with Age 2 years to 18 years (2nd month to 2nd year of life symptoms begin) and Transfusion dependent Thalassemia who got blood transfusion at least one year were included in this study. The patients with newly diagnosed thalassemia without having blood transfusion less than one year and Guardians of the subjects who did not provide written consent to participate in the study were excluded in this study.

Main outcome variables were Height for age, Weight for age, Weight for height, BMI Chart, SMR grouping, Serum ferritin. Transfusion dependent thalassaemia defined those who require life- long regular blood transfusion.[8]

i) Beta thalassemia major was defined as patients with no detectable beta chain synthesis due to absent beta chain messenger RNA and Hb electrophoresis shows

β thal$^+$: Hb A: 10-90%, Hb A2: 1.5-40%, Hb F: 10-90%

β thal^{0}Hb A: 0, Hb A2: 1.5-4%, Hb F: 98%.[9]

ii) Hb E Beta thalassemia (Severe/transfusion dependent) was defined if patients present with the clinical symptoms of thalassemia major and Hb electrophoresis pattern.[10]

iii) Number of blood transfusion is definedas total numberof unit of blood transfused from initiation of transfusion till inclusion into the study.Typical programs involve transfusions of 10-15cc/kg 0f packed leukodepleted red cells.[11]

iv) Frequency of transfusion is defined as interval between two subsequent blood transfusions.

v) Nutritional status was assessed in terms of anthropometry like height for age and weight for age according to NCHS chart.[12]

vi) Serum ferritin level is considered high if ≥2000 ng/ml, but ≥1000 ng/ml is considered as a cutoff point to start chelation therapy.[5]

vii) Anemia : Children 6 - 59 months: Mild: 100-109 g/l, Moderate: 70-99 g/l, Severe: <70 g/l.[13]

viii) Stunting: Moderately stunting is defined by a height for age z score below -2 and severely stunting is defined height for age z score below -3SD.

ix) Wasting: Moderate wasting is defined by weight for height is between -2 to -3SD and severely stunting is defined weight for height is below -3 SD.[14]

x) a : Sexual Maturity Rating (SMR)[15] : Stages (Female).

SMR stage	Pubic hair	Breast
1	Preadolescent	Preadolescent
2	Sparse lightly pigmented	Breast and papilla elevated as small mound
3	Darker beginning to curl	Breast and areola enlarged
4	Coarse curly abundant	Areola and papilla formed secondary mound
5	Adult, feminine triangle	Mature nipple projects

SMR 1-2, Early adolescence, 3-5, Middle adolescence, 5, Late adolescence.

x) b : Sexual Maturity Rating (SMR): Stages (Male)

SMR stage	Pubic hair	Penis	Testes
1	None	Preadolescent	Preadolescent
2	Scanty long	Minimal change	Enlarge scrotum
3	Darker starting to curve	Lengthens	Larger
4	Resembled adult type	Larger	Larger scrotum dark
5	Adult distribution	Adult size	Adult size

Patients were selected purposively after getting the clinical diagnosis of thalassemia who was admitted in the Pediatric Hematology and Oncology unit and Hematology ward of CMCH and the patients were divided into two groups.

Group I: Patients who received blood transfusion >12 times per year.

Group II: Patients who received blood transfusion ≤12 times per year.

Study procedure was explained thoroughly about the aims, objectives and detail procedure of the study to the legal guardian of the patients and a written informed consent was taken. He/She was encouraged for voluntary participation and allowed freedom to withdraw from the study whenever he/she liked even after participation. From all eligible subjects after getting consent, asked regarding the starting time of first transfusion, number of blood transfusion received previously and details about haemolyticanaemia were noted. Five cc of venous blood was collected and send for analysis of serum ferritin and to see the pre transfusion Hb. All physical growth parameters like height, weight, BMI, delayed puberty, SMR, Hb level, serum ferritin, were recorded. Stadiometer, Bathroom scale, measuring tape, 5 cc disposable syrnge, butterfly needle, sterile test tube, and standard lab facility were used as equipments. All biochemical tests were done in the laboratory of CMCH and Chevron Clinical Laboratory, Chattogram.

All relevant data were noted in the pre tested data collection form. All data were checked and rechecked to avoid omission and error. Cost was born by the researcher herself.

All data was checked and edited after collection. Then the data were entered into computer statistical analysis of the results being obtained by using windows based computer software devised with SPSS-22.0. All data was evaluated by using statistical methods-Chi-square test and t-test. The results were presented in tables and figures. The statistical terms were included in this study is mean, standard deviation, percentage. Statistical significance was set at $p<0.05$ and confidence interval set at 95% level.

Ethical Committee approval (Memo No. CMC/PG/2015/241) was duly obtained from the Institutional Review Board of Chittagong Medical College Hospital, Chattogram prior commencement of the study.

Results
In this present study, 53.3% patients were female in group I and 43.3% in group II. Male and female ratio was 1:1. Among them, 13.3% patients had consanguinity in group I and not found in group II. In this study, it was observed that the mean serum ferritin was 1243.77±761.626 in group I and 293.77±142.686 in group II which was significantly ($p<0.05$) increased in group I (Table I).Distribution of the study patients by pattern of height for age showed that almost two third (60.0%) patients had severely stunted in group I and 8(26.7%) in group II which was statistically significant ($p<0.05$) (Table II). Pattern of weight for age of the study patients revealed that majority (93.3%) patients had under weight (<-2SD) in group I and 18(60.0%) in group II and the difference was statistically significant ($p<0.05$) (Table III). Distribution of the study patientsaccording to BMI Chart, it was observed that more than one third (36.7%) patients had underweight in group I and 6(20.0%) in group II (Not shown). Sexual Maturity Rate (SMR) grouping of the study patients showed that more than two third (69.6%) patients had SMR 1-2 in group I and 17(94.4%) in group II (Table V). Distribution of serum ferritin by pattern for height for age showed that almost two third patients had severely stunted in patients who had mean serum ferritin level was (Mean±SD) 1243.77±761.626 and 8(26.7%)in patients who had serum ferritin level (Mean±SD) 293.77±142.666.The difference was statistically significant ($p<0.05$)(table VI).Distribution of serum ferritin level by pattern of weight for height (n=60), Table VII shows pattern of weight for height of patients of serum ferritin level (Mean±SD) 1243.77±761.626.It was observed that 5(16.7) patients had moderately wasted in (Mean±SD)1243.77±761.626 and 2(6.7%) in (Mean±SD)293.77±142.626.The difference was statistically not significant ($p>0.05$).

Table I : Distribution of the study patients by serum ferritin(n=60)

	Group-I (n=30) Mean±SD	Group-II (n=30) Mean±SD	p value
Serum ferritin	1243.77±761.626	293.77±142.686	0.001[s]

s= significant, p value reached from unpaired t-test.

Table I shows that the mean serum ferritin was 1243.77±761.626 in group I and 293.77±142.686 in group II. The difference was statistically significant ($p<0.05$) between two groups.

Table II : Distribution of the study patients by pattern of height for age (n=60)

Height for age	Group-I (n=30)		Group-II (n=30)		p value
	n	%	n	%	
Severely stunted	18	60.0	8	26.7	0.027[s]
Moderately stunted	8	26.7	12	40.0	
Normal	4	13.3	10	33.3	

s= significant, p value from Chi square test.

Table II shows that almost two third (60.0%) patients had severely stunted in group I and 8(26.7%) in group II. The difference was statistically significant (p<0.05).

Table III : Distribution of the study patients by pattern of weight for age (n=60)

Weight for age	Group-I (n=30)		Group-II (n=30)		p value
	n	%	n	%	
Under weight (<-2SD)	28	93.3	18	60.0	0.002[s]
Normal	2	6.7	12	40.0	

s= significant, p value reached from Chi square test.

Table III shows that majority (93.3%) patients had under weight (<-2SD) in group I and 18(60.0%) in group II. The difference was statistically significant (p<0.05) between two groups.

Table IV: Distribution of the study patients by pattern of weight for height (n=60)

Weight for height	Group-I (n=30)		Group-II (n=30)		p value
	n	%	n	%	
Severely wasted	1	3.3	1	3.3	0.481[ns]
Moderately wasted	5	16.7	2	6.7	
Normal	24	80.0	27	90.0	

ns= not significant, p value reached from Chi square test.

Table IV shows pattern of weight for height of the study patients, it was observed that 5(16.7%) patients had moderately wasted in group I and 2(6.7%) in group II. The difference was statistically not significant (p>0.05) between two groups.

Table V : Distribution of the study patients by Sexual Maturity Rate (SMR) grouping (n=41)

SMR grouping	Group-I (n=23)		Group-II (n=18)		p value
	n	%	n	%	
SMR 1-2	16	69.6	17	94.4	0.132[ns]
SMR 3-5	6	26.1	1	5.6	
SMR >5	1	4.3	0	0.0	

ns= not significant, p value reached from Chi square test.

Table V showed Sexual Maturity Rate (SMR) grouping of the study patients. It was observed that more than two third (69.6%) patients had SMR 1-2 in group I and 17(94.4%) in group II. The difference was statistically not significant (p>0.05).

Table VI : Distribution of serum ferritin by pattern of height for age(n=60)

Height for age	Serum ferritin (n=30) (Mean±SD) 1243.77±761.626		Serum ferritin (n=30) (Mean±SD) 293.77±142.686	
	n	%	n	%
Severely stunted	18	60.0	8	26.7
Moderately stunted	8	26.7	12	40.0
Normal	4	13.3	10	33.3

p value=0.027[s].

Table VI shows almost two third patients had severely stunted in patients who had mean serum ferritin level was (Mean±SD) 1243.77±761.626 and 8(26.7%)in patients who had serum ferritin level (Mean±SD) 293.77±142.666.The difference was statistically significant (p<0.05).

Table VII : Distribution of serum ferritin level by pattern of weight for height (n=60)

Weight for height	Serum ferritin (n=30) (Mean±SD) 1243.77±761.626		Serum ferritin (n=30) (Mean±SD) 293.77±142.636	
	n	%	n	%
Severely wasted	1	3.3	1	3.3
Moderately wasted	5	16.7	2	6.7
Normal	24	80.0	27	90.0

p value=0.481[ns].

Table VII shows pattern of weight for height of patients of serum ferritin level (Mean±SD) 1243.77±761.626.It was observed that 5(16.7) patients had moderately wasted in (Mean±SD) 1243.77±761.626 and 2(6.7%) in (Mean±SD) 293.77±142.626.The difference was statistically not significant (p>0.05).

Discussion

In this present study, male to female ratio was 1:1. This was Similar to study done by Moiz et al.[16] But male predominant were observed by Simhachalam et al and Jameel et al.[17,18]

In our study, it was observed that the mean serum ferritin was 1243.77±761.626 in group I and 293.77±142.686 in group II. The mean serum ferritin level was significantly (p<0.05) increased in

group I. Gomber and Dewan showed Mean hemoglobin and ferritin did not affect growth significantly.[19] But Pemde et al. showed mean ferritin levels were significantly higher in patients with short stature than in the patients with normal height.[5] An increase of 3571 units of serum ferritin was associated with a decrease of one point in height z-scores. One-fifth of adolescent patients had delayed puberty.[5] Studies by Shaana; Carnelli et al.found that serum ferritin were significantly correlated to total amount of blood transfusions.[20,21] Frequent blood transfusion has led to iron overload with many complications the commonest of which is growth failure. A study from Israel Shalitin et al found that high serum ferritin levels (>3000 ng/mL) during prepubertal age were related to final short stature.[22] Another study from Malaysia revealed that the mean serum ferritin level of thalassemics with a height under the third percentile was higher compared with those with a height over the third percentile (4567.0 ng/mL vs 2271.0 ng/mL, p<0.05).[23] Saxenareported that lower BMI at older ages depicting negative inter-relationship between serum ferritin and body mass index.[24] Another study by Hamidah et al. also showed mean serum ferritin levels were better (2271.0 ng/ml) in patients with height over the third percentile than in patients with height lower than the third percentile (4567.0 ng/ml, p<0.05).[23] In this study, it was observed that 60.0% patients had severely stunted in group I and 26.7% in group II. The difference was statistically significant (p<0.05) between two groups. A study showed that the thalassemia patients were short, had low rate of growth and BMI and this was due to either delayed or absent pubertal spurt, which was related to low haemoglobin and high ferritin levels and sub-optimal iron chelation therapy.[24] It was observed that the growth faltering sets in at a much younger age and becomes apparent by 8 years of age. Poor socioeconomic background compounds the problem. A study from Egypt reported, height z-scores of <2 in 49.0 patients.[25] Although growth stunting commences in early years of life in thalassemia, growth retardation becomes more apparent with their advancing age.[16,26] Pemde et al. found 33.11% of their patients had short stature, and 24.19% of their patients were thin or severely thin.[5] Height-for-age was related to mean ferritin levels and not to mean pretransfusion Hb levels. This suggests that it is not chronic hypoxia (By anemia) but excess iron that is responsible for short stature.

In this study, 93.3% patients had under weight (<2SD) in group I and 60.0% in group II. The difference was statistically significant (p<0.05) between two groups. A study from Egypt reported that weight z-scores of <2 in 47.0% patients.[25]

This current study observed that 16.7% patients had moderately wasted in group I and 6.7% in group II. The difference was statistically not significant (p>0.05) between two groups. In this present study, it was observed that 36.7% patients had underweight in group I and 20.0% in group II. Underweight was higher in group I but the difference was not statistically significant (p>0.05) between two groups. Study by Sheikh et al showed that most (58.69%) of the thalamic patients were underweight.[27] Statistically significant association of nutritional status with age of thalamic patients and duration of illness was detected. Tienboon et al. showed 64% and 78% underweight males and females respectively in their work.[28]

An assessment of Sexual Maturity Rating (SMR) was done in all the patients 10 years or older. In this current study, it was observed that 69.6% patients had SMR 1-2 in group I and 94.4% in group II. The difference was statistically not significant (p>0.05) between two groups. Study by Pemde et al showed only a small number of patients had delayed puberty, which was diagnosed clinically by SMR ratings only.[5]

Limitations

i) The study was for short duration and single centered.

ii) The small sample size for subgroups of TDT which might distort the result of statistical analysis.

iii) All the lab investigations were not supported by single centre.

iv) The effects of other factors such as hormonal status and endocrinopathies on growth and their exact association with serum ferritin levels need to be determined in a meticulous manner. This could not be done in this study due to the expensive nature of hormonal testing.

Conclusion

Increase blood transfusion increases serum ferritin level seen in all the patients and out of this patients 60% was severely stunted which is statistically significant.

Recommendation

i) To reduce the serum ferritin so that related complication could be avoided.

ii) Large scale multicenter study with nationally representative sample.

iii) Early intervention by appropriate chelation therapy may help for normal growth progression.

iv) The information gathered from this study was of utmost benefit in developing nutritional recommendations to improve nutritional status, growth, quality of life and treatment in the children with thalassemia major.

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Contribution of authors

RK: Conception, acquisition of data, interpretation of data, drafting and final approval.

GMTA: Design, data acquisition, critical revision & final approval.

AKD: Drafting analysis revision of content & final approval.

TB: Design analysis, critical revision & final approval.

MK: Data acquisition, drafting & final approval.

ZC: Data acquisition, analysis, critical revision & final approval.

Disclosure

All the authors declared no conflict of interest.

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