“TO ASSESS GROWTH AND DEVELOPMENT IN BETA-THALASSEMIC CHILDREN BASED ON THEIR TRANSFUSION AND CHELATION THERAPY STATUS”

Pediatrics

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ABSTRACT

Introduction: β -thalassemia is one of the most common transfusion dependent genetic disorders with consequences of transfusions or chelation therapy especially effecting on growth and development of these patients.

Aims and objectives: To assess growth and development in β -thalassemic children based on their transfusion and chelation therapy status.

Methodology: The clinical and socio-demographic data was collected from the β -thalassemia (n=52) patients (2-15 years of age) included in the study using predesigned proforma. Data and blood reports relevant to the study were collected and analysis was done by SPSS software v 22.0 applying non-parametric Man-Whitney U Test, chi-square tests for independence of attributes.

Results: Growth retardation is significantly more in beta-thalassemia major patients (45.95%) than minor forms of beta-thalassemia (13.33%). Patients without chelation therapy and those having transfusions $\leq$ once monthly were associated with growth retardation ($p < 0.05$). A range of 5 - 12% patients were having subnormal IQ and SQ whereas 41.2% were diagnosed as Suspects by DDST-II.

Conclusion: A significant number of β -thalassemia major patients were having inadequate transfusion and chelation therapy which affect their growth and development variably compared to β -thalassemia minor patients.

KEYWORDS

β -thalassemia major, growth and development, Intelligence Quotient, Social Quotient, transfusion, chelation

INTRODUCTION:

Thalassemia is a group of genetic disorders of quantitative globin chain production of hemoglobin (1-2). Every year around 100,000 pediatric patients with thalassemia major are born world over, of which 10% are contributed by India (3). The carrier rate is much higher in North India (3-15%) than Southern part (1-3%); while the communities like Sindhis, Lohanas, Bhanushalis etc carry much higher prevalence than others (4,5).

Blood transfusion dependency does act as a double-edged sword for the patients. Inadequate transfusion protocols can have anemia related health problems; and multiple transfusions can hamper with iron overload (6). To those chelation therapy for iron overload works as a life saviour, but with its own complications. Growth of the β -thalassemia major patients has been affected by growth hormone deficiency, hypothyroidism and delayed sexual maturation (7-9). The effect of multiple blood transfusions and chelation therapy over development and intellectual ability of these patients is less explored in literature.

METHODOLOGY:

This cross-sectional study was conducted at the department of Pediatrics, Shyam Shah Medical College and Gandhi Memorial Hospital Rewa. A structured proforma was used for every β -thalassemia child enrolled after obtaining consent from parents. Out of 56 patients, 4 patients were dropped out from the study group (two were dead and two were lost to follow up). So this study was conducted on 37 transfusion dependent beta-thalassemia (TDT) major patients and 15 non-transfusion dependent beta thalassemia (NTDT) patients. Serum ferritin level and hemoglobin level was checked before blood transfusion during the study period.

Anthropometric assessments were plotted in age-appropriate standard growth charts to determine their respective centiles. For growth retardation parameters were included weight for age ($\leq$ 3rd centile), height for age ($\leq$ 3rd centile), weight-for-height ($<$ 2 SD) and BMI (body mass index $\leq$ 5th centile). Then we correlated the results with different variables representing adequacy of transfusion therapy or chelation therapy.

Development of each child was assessed using following age appropriate tests whichever was applicable.

1. Seguin Form Board test: 10 blocks were taken out and stacked in

front of the child who had to put them back as quick as possible. The task was repeated three times and the score was the time taken on the fastest trial. The age group was 3 years to 15 years according to the norms for Seguin Form Board test.

2. Denver Developmental Screening test: For age group of 2 yrs to 6 years, this test is consisting of 125 items to screen the following areas of function: Personal-social, Fine-motor-adaptive, Language, Gross-motor. Materials required were available in the department. The results were interpreted as NORMAL (no delays and a maximum of 1 caution), SUSPECT (two or more cautions and/or one or more delays) and UNTESTABLE (refusal scores on one or more items completely).

3. Draw-A-Man Test: for age group of 4 years to 15 years, sex specific scoring system of this test was administered as per manual with total number of 25 scoring points in a man drawn by the child.

4. Vineland Social Maturity Scale (VSMS): For children aged 2 yrs to 15 years, we used VSMS record sheet with total of 89 test items to assess 8 profile to analyze namely self help general, self help eating, self help dressing, self direction, occupation, communication, locomotion, socialization. Then Social Quotient and Intelligence Quotient was calculated by the formula: (Mental age/ Chronological Age X 100%).

STATISTICAL ANALYSIS:

Data were entered into Microsoft Excel 2007 and was analyzed using IBM SPSS statistics version 22.0 by appropriate statistical tests including non-parametric Man-Whitney U test, and chi-square tests for independence of various attributes at 95% confidence level. A value of $P < 0.05$ was considered as statistically significant. Categorical variables were represented by frequency and percentages whereas quantitative variables are represented by mean $\pm$ SD, wherever applicable.

RESULTS:

Out of 52 cohorts, 71.15% were transfusion-dependent beta-thalassemia (TDT) major patients and 55.8% were male. 28.85% cases were from outside of Rewa district. Mean age of TDT major patients was 70.22 ± 38.05 months, whereas mean age of non-TDT patients was 128.47 ± 23.56 months. Most of the patients were of age group below 10 years (67.30%) and of lower middle socio-economic class (75%).

Among beta-thalassemia major patients, male and female ratio was 1.3:1 and 81% of them belonging to age group less than 10 years. Mean

pre-blood transfusion hemoglobin level 6.9 ± 1.62 gm% and 48.64% cases had total more than 100 times transfusions. Only 13.51% of them were maintaining hemoglobin level ≥ 9 gm% as per moderate blood transfusion regimen. 78.37% were under chelation therapy (100% oral chelation) and 45.94% were transfused in a frequency of only once in a month. Only 24.32% were able to maintain serum ferritin level below 1000 mg/dl at then dose of chelation and frequency of blood transfusion.

Patients under chelation therapy were less associated with growth retardation ($p < 0.05$). Patients whose pre-blood transfusion hemoglobin level < 9 gm% had more growth retardation ($p < 0.05$). Patients who had blood transfusion $\leq$ once in a month had more growth retardation ($p < 0.05$). No statistically significant association found between serum ferritin level and total number of blood transfusions with growth retardation ($p > 0.05$). We found more of those patients suffering from β thalassemia major had growth retardation compared to those who suffering minor form of β thalassemia ($p < 0.05$).

With age-appropriate IQ screening tests we found 5.4% by Vineland Social Maturity Scale, 12.5% by Draw-A-Man test and 6.25% by Seguin Form Board Test were having subnormal Intelligence. Whereas 41.2% of children screened by Denver II developmental Screening Test were diagnosed as Suspects and admired for further confirmatory tests. There was no significant association of patients with subnormal IQ among beta-thalassemia patients $p > 0.05$

Table 1: Basic characteristics of study cohort.

Type of thalassemia	TDT Major		NTDT	
	Frequency	Percentage	Frequency	Percentage
1) Gender				
Male	21	56.76%	8	53.33%
Female	16	43.24%	7	46.67%
2) Age				
2-6 years	17	45.94%	0	0
7-10 years	14	37.83%	4	26.67%
>10 years	6	16.21%	11	73.33%
3) Socioeconomic class				
Lower middle class	25	67.57%	14	93.33%
Upper lower class	8	21.62%	1	6.67%
Lower class	4	10.81%	0	0
4) Total number of blood transfusions				
≤ 50	14	37.83%	15	100%
51-100	5	13.51%	0	0
101-150	9	24.32%	0	0
151-200	6	16.21%	0	0
≥ 200	3	8.1%	0	0
5) Growth retardation				
(a) Weight for age				
$\leq 3^{\text{rd}}$ centiles	17	45.94%	2	13.33%
$> 3^{\text{rd}}$ centiles	20	54.05%	13	86.67%
(b) Height for age				
$\leq 3^{\text{rd}}$ centiles	16	43.24%	2	13.33%
$> 3^{\text{rd}}$ centiles	21	56.75%	13	86.67%
(c) Weight for height				
$\leq -2SD$	8	53.33%	NA	NA
$> -2SD$	7	46.67%	NA	NA
(d) Body mass index				
$\leq 5^{\text{th}}$ centiles	2	9.09%	0	0
$> 5^{\text{th}}$ centiles	20	90.9%	15	100%
6) Tests for intelligence (age appropriate)				
(a) Seguin form Board test				
IQ $\geq 90\%$	23	71.87%	15	100%
IQ 80-89%	7	21.88%	0	0
IQ $< 80\%$	2	6.25%	0	0
(b) Draw-A-man test				
IQ $\geq 90\%$	14	58.33%	14	93.33%
IQ 80-89%	7	29.17%	1	6.67%

Table 2: Relation of growth retardation with adequacy of transfusion and chelation therapy among transfusion dependent beta-thalassemia major patients

		Growth retardation	No growth retardation	p- value
1) Chelation Therapy	Yes	10	19	0.008
	No	7	1	
2) Serum ferritin Level	< 1000 mg/dl	7	2	0.069
	≥ 1000 mg/dl	10	18	
3) Pre-blood transfusion hemoglobin	< 9 gm%	17	15	0.027
	≥ 9 gm%	0	5	
4) Frequency of Transfusions	$\geq$ Twice a Month	2	12	0.0075
	$\leq$ Once a month	15	8	

Table 4: Relation of subnormal IQ with adequacy of transfusion and chelation therapy among transfusion dependent beta-thalassemia major patients

		Subnormal IQ	Normal IQ	p- value
1) Chelation Therapy	Yes	8	20	0.403
	No	1	8	
2) Serum ferritin Level	< 1000 mg/dl	2	5	1.0
	≥ 1000 mg/dl	7	23	
3) Pre- blood transfusion hemoglobin	< 9 gm%	9	21	0.160
	≥ 9 gm%	0	7	
4) Frequency of Transfusion	$\geq$ Twice a Month	3	12	0.711
	$\leq$ Once a month	6	16	

Table 5: Relation of growth retardation and subnormal IQ with severity of thalassemia patients based on dependence of blood transfusions

	Beta-thalassemia major	Beta-thalassemia minor	p-value
Growth retardation	17	2	0.0312
No growth retardation	20	13	
Subnormal IQ	8	1	0.145
Normal IQ	26	14	

CONCLUSION:

By the present study, we can conclude that majority of transfusion-dependent beta- thalassemia major patients are inadequately transfused with their present blood transfusion strategy including frequency of transfusions monthly. There was inadequacy of chelation therapy resulting majority of these patients unable to maintain serum ferritin level below 1000 mg/dl. A wide number of cases had growth retardation which was significantly related with inadequacy of transfusion and chelation therapy among β -thalassemia major compared with β -thalassemia minor patients. Suspects screened by DDST-II tool are warranted for confirmatory tests, and patients with subnormal IQ or SQ were determined by age appropriate tests. But there was no significant relation found between patients with subnormal IQ and inadequacy of transfusion or chelation therapy. Regular screening with serial measurements of growth and development are required for management of complications among beta-thalassemia patients. Institutional thalassemia management strategy can be revised for adequate transfusion and chelation therapy periodically.

Limitations:

1. Small sample size
2. Short duration of study
3. Confirmatory tests for development assessment

What is Already Known?

1. Growth and development are affected in transfusion-dependent β -thalassemia

What this Study Adds?

1. Growth and development of the patients with transfusion dependent β -thalassemia major are more affected than non-transfusion dependent β -thalassemia patients
2. Inadequate transfusion and chelation therapy related to growth retardation but not to subnormal IQ of the TDT patients

REFERENCES:

1. Borgna-Pignatti C, Galanello R, Thalassemias and related disorders: quantitative disorders of haemoglobin synthesis, Wintrobe's Clinical Hematology, 13th Edition, chapter 34.862-912
2. Cunningham MJ, et al. The thalassemias, Nathan and Oski's Hematology of infancy and childhood, 7th Edition, chapter 20, 1015-1107
3. Yaish HM. Medscape. Fact sheet: Pediatric Thalassemia, 2017. Available at: <https://emedicine.medscape.com/article/958850-overview>. Accessed 6 August 2007.
4. Colah R, Italia K, Gorakshakar A, Burden of thalassemia in India: The road map for control, *Ped Hematol Oncol J* 2, 2017;79-84
5. Dangr CBS, Kaur M, et al. Burden of Haemoglobinopathies in Madhyapradesh, Central India. *International Journal of Biotechnology*. 2013. Photon 111, 224-242.
6. Shah N, Mishra A, Chauhan D, Vora C, Shah NR, study on effectiveness of transfusion program in thalassemia major patients receiving multiple blood transfusions at a transfusion centre in Northern India. *Asian J Transf Sci* – vol 4;2;2010; 94-98
7. Roth C, Pekrun A, Bartz M, Jarry H, Eber S, Lakomek M, Scroter W. Short stature and failure of pubertal development in thalassemia major; evidence of hypothalamic neurosecretory dysfunction of growth hormone secretion and defective pituitary gonadotropin secretion. *Eur J Pediatr* 1997;156: 777-783
8. De Virgiliis, et al. Deferoxamine-induced growth retardation in patients with thalassemia major. *J Pediatr* 1988;113: 661-669
9. Wonke B. Clinical management of β -thalassemia major. *Semin Hematol* 2001;38: 350-359
10. Shalitin S, et al. serum ferritin level as a predictor of impaired growth and puberty in thalassemia major patients. *Eur J Haematol* 2005; 74: 93-100
11. Gattermann N. Guidelines on iron chelation therapy in patients with myelodysplastic syndromes and transfusional iron overload. *Leuk Res* 2007;31:S10-5
12. Cazzola M, Borgna-Pignatti C, Locatelli F, Ponchio L, Beguin Y, De Stefano P. A moderate transfusion regimen may reduce iron loading in beta- thalassemia major without producing excessive expansion of erythropoiesis. *Transfusion* 1997;37:135-40.
13. Porter J, Viprakasit V. Iron overload and chelation. Guidelines for the management of transfusion dependent thalassemia. *Thalassemia International Federation 3rd Edition* (2014);chapter: 42-89
14. Borgna-Pignatti C et al. survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. *Haematological* 2004; 89: 1187-93
15. Origa R. et al. Current growth patterns in children and adolescents with thalassemia major. *Blood*, 2016;128:2580-82
16. Dhoub NG, et al. Growth and Endocrine function in Tunisian Thalassemia Major Patients. *Mediterr J Hematol Infect Dis* 2018;10:1-9, e2018031
17. Yassin MA, Soliman AT, Sanctis VD, Yassin KS and Abdulla MAJ. Final height and endocrine complications in patients with beta-thalassemia intermedia: our experience in non-transfused versus infrequently transfused patients and correlations with Liver Iron Content. *Mediterr J Hematol Infect Dis* 2019; 11: e2019026
18. Agrawal MB, et al. Antibody to hepatitis C virus in multi-transfused thalassemics-Indian experiences. *J Assoc Physicians India* 1993;41: 195-7
19. Arankalle VA, Chadha MS, Jha J, Amrapurkar DN, Banerjee K. Prevalence of anti-HCV antibodies in western India. *Indian J Med Res* 1995;101:91-3
20. Kiani RA, Anwar M, Waheed U, Asad MJ, Abbasi S, and Zaheer A. Epidemiology of transfusion transmitted infection among patients with beta-thalassemia major in Pakistan. *Journal of Blood Transfusion* 2016; 1-5.
21. Sanctis VD, et al. Endocrine profile of β -thalassemia major patients followed from childhood to advanced adulthood in a tertiary care center. *Indian Journal of Endocrinology and Metabolism* 2016;20(4): 451-59