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To assess the effect of blood transfusion and chelation therapy on growth and development of transfusion-dependent beta-thalassemia patients in a rural setting of central India

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Abstract
Background: Beta-thalassemia major is one of the most severe life-long transfusion-dependent anemias. Clinical features vary from those due to disease itself to those due to consequences of transfusions or chelation therapy, especially affecting the growth and development of these patients.
Method: A total 37 patients (aged 2 years to 15 years) were included for this cross sectional study to assess the effect of transfusion and chelation therapy on growth and development of transfusion-dependent beta-thalassemia patients (TDT) in a rural setting of central India. Data and blood reports were collected from January 2019 and was analyzed using SPSS v 22.0 applying non-parametric Man-Whitney U test and Chi Square test for independence of attributes.
Findings: Only 5 (13.5%) were adequately transfused maintaining pre-blood transfusion hemoglobin level ≥9gm% and all of them did not have growth retardation. A total 29 patients were under chelation therapy, and 28 (96.55%) were found to have serum ferritin level ≥1000mg/dl. Growth retardation was diagnosed among 17 (45.94%) of the patients, whereas a range of 5-12% of them were having Intelligence Quotient (IQ) or Social Quotient (SQ) <80% as assessed by Seguin form board test, Draw-a-man Test and Vineland Social Maturity Scale. 7 out of 17 patients who were below 6 years of age, were diagnosed as suspects by Denver Developmental Screening tool.
Conclusion: A significant number of transfusion-dependent Beta-thalassemia patients were having inadequate transfusion and chelation therapy which affect their growth and development variably (positively corelated if P <o.o5).

Keywords: Transfusion-dependent beta-thalassemia, chelation therapy, growth and development, intelligence quotient

Introduction

Being the most common hereditary hemoglobinopathy worldwide, Thalassemia is a group of genetic disorders of quantitative globin chain production with a resultant of inadequate or excess α-globin and β-globin chains of hemoglobin inside red blood cells [1, 2]. Every year approximately 100,000 children with thalassemia major are born world over, of which 10% are contributed by India. In addition to 65,000-67,000 beta-thalassemia patients in India, around 9,000-10,000 cases are added more every year [3]. In India, the carrier rate is much higher in Northern states (3-15%) than Southern part (1-3%); while the communities like Sindhis, Lohanas, Bhanushalis, Vellalas etc hold much higher prevalence than others [4].The percentage of people with hemoglobinopathies including β-thalassemia in Madhyapradesh is 16% [5].

Lifelong blood transfusion dependency acts as a double-edged sword for them. Inadequate transfusion therapy has anemia related health problems; and multiple transfusions can result into iron overload. Even risk of acquiring transfusion transmitted infections (TTIs) mainly Human Immunodeficiency Virus (HIV), hepatitis B (HBV) and hepatitis C virus (HCV) is higher. In a nut, these patients seldom live through adulthood [6]. Chelation therapy for iron overload works as a life saviour, but with its own complications. Growth of the β-thalassemia major patients has been studied to be affected by growth hormone deficiency, hypothyroidism and delayed sexual maturation [7-9]. Endocrinopathies due to iron overload in β-thalassemia major are well established in literature with less frequent prevalence of hypothyroidism, hypoparathyroidism, and diabetes mellitus [10-14].

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The effect of multiple blood transfusions and adequacy of chelation therapy over development and intellectual ability of these patients is least studied and explored.

Materials and Methods
This was a cross sectional study, conducted at the department of Pediatrics, Shyam Shah Medical College and Gandhi Memorial Hospital Rewa (MP) from January 2019 with ethical permission. All cases aged 2 years to 15 years of beta-thalassemia diagnosed by High Performance Liquid Chromatography (HPLC) and who had at least 10 or more blood transfusions before this study were included.

A structured proforma was used for every child enrolled after obtaining consent from parents. 37 transfusion dependent beta- thalassemia (TDT) major patients were investigated with socio-demographic history and clinical examination, including anthropometric measurements. Prior to transfusion blood samples of the patients were collected for complete blood count and serum ferritin level. Recent chelation therapy status were noted.

To assess adequacy of multiple blood transfusions among TDT patients, we considered pre-blood transfusion hemoglobin <9 gm% as the cut off level for inadequately transfused patients at the time of data collection as per the moderate transfusion regimen.

To assess adequacy of iron chelation therapy we correlated recent dose of iron chelation and serum ferritin level monitored; in context to frequency of monthly blood transfusions. The cut off level was serum ferritin level ≥1000 mg/dl for inadequately chelated patients.

Anthropometric assessments were plotted in age-appropriate standard growth charts to determine their respective centiles. For growth retardation parameters were included weight for age (≤ 3rd centile), height for age (≤ 3rd centile), weight-for-height (<-2 SD) and BMI (body mass index ≤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 ± SD, wherever applicable.

Results
Total 37 patients were included and the mean age was 70.22 ± 38.05 months (5.85 ± 3.17 years). Only 5(13.5%) were maintaining pre-blood transfusion hemoglobin level ≥ 9gm% and all of them did not have growth retardation. Total 29 patients were under chelation therapy, and 28 (96.55%) were found to have serum ferritin level ≥ 1000 mg/dl which we have considered as inadequately chelated. Growth retardation was diagnosed among 17 (45.94%) of the patients. 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 ≤ 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 ($p>0.05$).

With age-appropriate IQ 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 IQ <80. Whereas 7 out of 17 patients who were below 6 years of age, were diagnosed as suspects by Denver Developmental Screening tool and were admired for further confirmatory tests. There was no significant association of patients with IQ <80% and ≥80% among transfusion-dependent beta-thalassemia patients ($p>0.05$).

Table 1: Basic characteristics of study cohorts

Type of thalassemia	TDT Major	
	Frequency	**Percentage**
1) Gender		
Male	21	56.76%
Female	16	43.24%
2) Age		
2-6 years	17	45.94%
7-10 years	14	37.83%
>10 years	6	16.21%

3) Socioeconomic class		
Lower middle class	25	67.57%
Upper lower class	8	21.62%
Lower class	4	10.81%
4) Total number of blood transfusions before the study		
≤ 50	14	37.83%
51-100	5	13.51%
101-150	9	24.32%
151-200	6	16.21%
≥ 200	3	8.1%
5) Growth retardation		
(a) Weight for age		
≤3rd centiles	17	45.94%
>3rd centiles	20	54.05%
(b) Height for age		
≤3rd centiles	16	43.24%
>3rd centiles	21	56.75%
(c) Weight for height		
<-2SD	8	53.33%
≥-2SD	7	46.67%
(d) Body mass index		
≤5th centiles	2	9.09%
>5th centiles	20	90.9%
6) Tests for intelligence (age appropriate)		
(a) Seguin form Board test		
IQ ≥90%	23	71.87%
IQ 80-89%	7	21.88%
IQ <80%	2	6.25%
(b) Draw-A-man test		
IQ ≥90%	14	58.33%
IQ 80-89%	7	29.17%
IQ <80%	3	12.5%
(c) Vineland social maturity scale		
SQ ≥90%	27	72.97%
SQ 80-89%	8	21.62%
SQ <80%	2	5.4%
7) Denver II developmental screening test		
Normal	10	58.82%
Suspects	7	41.17%

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	<9gm%	17	15	0.027
	≥9gm%	0	5	
4) Frequency of transfusions	≥ Twice a Month	2	12	0.0075
	≤Once a month	15	8	

Table 3: 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	< 9gm%	9	21	0.160
	≥ 9gm%	0	7	
4) Frequency of transfusion	≥Twice a Month	3	12	0.711
	≤Once a month	6	16	

Discussion

Adequacy of transfusion was determined in Shah *et al* 2010 by considering 10 gm% by setting pre-transfusion hemoglobin 10 gm% as the cut off ; percentages of these receiving 1, 2, 3, and 4 transfusions per month were 62%, 50%, 43% and 50% respectfully [15]. In our study we set the cut off at 9 gm% according to moderate transfusion regimen [18]. Mean hemoglobin level was 6.9 ± 1.62 gm%. Only 5 patients were maintaining pre-transfusion hemoglobin level above 9 gm%, rest were under-transfused.

Thalassemia International Federation Guidelines recommend that chelation therapy is initiated when serum ferritin levels rises above 1000 mg/dl, or after 10-20 blood transfusions or, after 2nd years of age [19]. Adequacy of chelation therapy was determined by expected serum ferritin levels to be maintained within normal limits i.e. below 1000 mg/dl irrespective of the total number of transfusions; whereas irregularity of chelation or its response [17]. In our study, 29 patients (78.37% of TDT patients) were under chelation therapy. Only 9 patients were maintaining serum ferritin level below 1000 mg/dl comprising 24.3% cases among TDT patients, which is higher than Shah's study [15]. It was found better outcomes with chelation therapy maintaining ferritin level below 1000 mg/dl [20].

There's no clear-cut minimum age for initiating chelation therapy in TDT patients to prevent growth and development defects [5]. Shalitin studied 39 thalassemia major patients between 1970 and 2002 with follow up for growth and endocrine complications. 36% cases were short stature (height ≤-2SD); whereas 56% patients had attained their final height by the end of the follow up. Mean serum ferritin level was significantly higher in patients with a final short stature than those with a final height > -2SD. Final short stature was negatively associated with age at onset of chelation therapy [15]. Origa R .study 2019 comprises growth patterns of 245 patients with thalassemia major born after 1995 in Italy. 145 (59%) patients were with short stature i.e. height <-2SD. They concluded an eventual positive effect of oral chelators on growth did not seem to be sufficient if started after age 10 years [21]. Dhouib study2018, 57% cases found to have growth retardation (height ≤-2SD) and thirteen had delayed puberty. Growth hormone deficiency found in 35% cases [22]. Yassin study 2019 in Qatar found that final height <-2SD occurred in 25% of patients with no significant difference between non-transfused versus infrequently transfused beta- thalassemia intermedia patients [32]. In our study we found out of 37 patients, 17 of TDT (45.9%) patients had weight for age ≤3rd centiles, 16 of TDT (43.2%) had height for age ≤3rd centiles and only 2 patients had low BMI ≤5th centiles for age.

Samaneh HM (2015) assessed the intelligence quotient of children with β-thalassemia major and healthy counterparts in terms of Full, Verbal and Performance Scales of IQ using 12 subscales of Wechsler IQ test for children. Results indicated that children with β-thalassemia major had lower performances in Full and Verbal IQs. But, according to mean scores of the two groups and Wechsler's views on IQ classifications, this downfall is not necessarily considered as serious [19]. In our study, we used age-appropriate tests for IQ and SQ assessment and we found that 70-80% of patients were having IQ ≥ 90%, 15-20% of patients with IQ 80-89% and 5-12% of patients with IQ <80%. For under 6 years of age i.e. 17 out of 37 beta-thalassemia major patients were assessed by Denver Developmental Screening tool II. We found that 7 (41.2%) cases among them had a result as Suspects and were admired for confirmatory tests after subsequent follow up visits.

Conclusion

By the present study, we can conclude that majority of transfusion-dependent beta- thalassemia 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, but not associated with serum ferritin level. Suspects screened by Denver II tool are warranted for confirmatory tests on follow up visits, and patients with IQ or SQ <80% were determined by age appropriate tests. But there was no significant relation found between patients with lower IQ or SQ and inadequacy of transfusion or chelation therapy. Regular screening with serial measurements of growth, development and endocrine functions is essential for early detection of complications among beta-thalassemia patients; and Institutional recent thalassemia management strategy should be revised for adequate transfusion and chelation therapy by regularity of supply of medications and availability of blood products. More longitudinal studies are needed to offer support to these preliminary results.

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