Study of Different Treatment Schedules in Patients with Thalassemia Major and its Relation to Mineral, Trace Elements and Albumin Blood Level Among Them

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Abstract:

Background: The Thalassemias (the commonest monogenic diseases) are a family of inherited disorders of hemoglobin synthesis, The classic changes of untreated Thalassemia major are now regularly seen only in countries without resources to support long- term transfusion program. Our aims were to study the relation between treatment schedules, hemoglobin level, trace element, minerals and albumin level among group of Thalassemic patients.

Subject &Methods: Cross-sectional study was conducted for the period from August till December 2002, in the center for anemia of Mediterranean origin in Ibin-Al-Bildy hospital in Baghdad city, where 121 patients with Thalassemia major attending the center for transfusion were selected and tests were done for different serum levels of trace element, minerals, hemoglobin and albumin using standard methods

Results: The mean level of trace element, minerals albumin were all significantly lower among the sample of patients except copper which was significantly higher than normal mean. The desferrioxamine therapy negatively correlated with zinc, albumin and magnesium (significant) level. Vitamin C therapy negatively correlated with zinc (significant), selenium and magnesium. Follate therapy correlated significantly with albumin TIBC, and had non-significant negative correlation with copper, zinc, selenium, calcium and magnesium.

Conclusion & Recommendation: The study shows that majority of patients were of young age groups < 20 years of age with large proportion of them suffering growth retardation and abnormally low level of some studied trace element minerals and albumin suggesting the possibility of inaccurate treatment schedules. It is recommended that more centers for thalassemia are to be established in different areas in our country, with increase efficiency for treatment and follow up of patients, the need for newer therapy like stem cell transplantation, and to establishe programs based on carrier screening and counseling of couples at marriage, preconception or early pregnancy,

Key word: Treatment schedules in thalassemic patients, Relation to mineral and trace element level

Introduction

Thalassemia genes are remarkably widespread, and are believed to be the most prevalent of all human genetic diseases[1].The Thalassemias, are a family of inherited disorders of hemoglobin synthesis characterized by a reduced output of one or other of the globin chains of adult hemoglobin[2]. The estimated gene frequencies range from 5 to 10 percent in some areas[3]. They are likely to pose an increasing health problem for many developing countries during the early part of the new millennium[4]. In 1999 WHO has estimated the carrier frequency of β- Thalassemia in Iraq is about 3% and the annual births of homozygote of β-Thalassemia are about 571 patients/ year[5]. In Egypt, Thalassemia represents the commonest cause of haemolytic anemia, in multi-center studies, the carrier rate has been reported in the range of 9%-10%[6]. In Basra, a recent premarital study on couples attending the Public Health Laboratory revealed that prevalence of β- Thalassemia trait is about 4.6%[7].

The aim in this study is to assess the effect of treatment schedules on blood levels of some trace elements, minerals, and albumin in a sample of patients with Thalassemia major attending the center for anemia of Mediterranean origin in Abin-Al-bildy hospital in Baghdad city for blood transfusion.

Materials & Methods

A coss-sectional study was conducted during the period from August to December 2002 in the center for anemia of Mediterranean origin in Abin-Al-balady hospital, 121 patients with thalassemia major were randomly selected using convenient sampling and patients attending the center for blood transfusion. Well-studied questionnaire forms were used, blood samples for hemoglobin estimation (Hb) and estimation of various levels of mineral, trace elements and albumin were taken from all the studied sample, hemolyzed samples were discarded. The blood was left at room temperature for 10 minutes for clotting, centrifuged at 3000 rpm for 10 minutes, and then serum was separated and stored at -20°c until used.

Body mass index (BMI) was measured as weight (in kilograms) divided by the square of the height (in meters), was classified according to the International accepted range of BMI[8] as follows:

1-Under weight <18.5
2-Normal 18.5-24.9
3-Over weight 25-29.9
4-Obese 30.0-39.9
5-Extremely obese >40

Methods

Chemicals and reagents

All chemical and standard solutions used in this work were the highest analytical grade, and used without purification.

1-Trace elements and minerals were measured by flame atomic absorption spectrophotometry (Schimadzu AA 646). Dilution of the serum was made by deionized water according to the sensitivity of the atomic absorption spectrophotometer in order to avoid the viscosity and to decrease the interference of the protein in serum [9, 10, 11, 12, 13]

2-Albumin in serum was measured by Bromocresol Green (BCG) method [14].

3-Hemoglobin determination

The cyanomethaemoglobin using Drabkin test was applied [14].

Statistical analysis:

Frequency tables used, statistical tests were done using correlation test, chi-square test and t-test. P values < 0.05 were considered significant

Results:

Table (1) shows that 62 (51.2%) patients were below 10.0 years of age, mean age was 10.44 ± 6.35 years, and 115 (95%) patients were diagnosed before the age of 5 years. Eighty two (67.8%) patient were male and 39 (32.2%) female. Majority of patients were from Baghdad city, 16 (13.2%) from Diala, 11 (9.1%) from Wassit, 4 (3.3%) from Karballa, 2 (1.7%) from Salah-Aldeen,. Seventy eight (64.5%) patients were from urban and 43 (35.5%) from rural areas.As for blood groups, 36 (29.8%) of patients were having blood group A, B and O, while only 13 (10.7%) patients were having blood group AB, majority of patients 110 (90.9%) were Rh +ve and only 11 (9.1%) patients were Rh – ve. Eighty one (66.9%) patients had hemoglobin level 8- 10 g\100ml, while only 5 (4.1%) had Hb < 7.0g \100ml and 3 (2.6%) patients had Hb > 10.0 g \100ml mean HB was 8.4 ±1.12 g\ dl. Majority of patients 85 (70.2%) require blood transfusion every 2-4 weeks. As for desferrioxamine (DFO) therapy, majority of patients 75 (62.0%) have therapy more than 4 times / week, 39 (32.2%) have the therapy 3-4 times /week and only 7 (5.8%) have it less than 3 times / week.Sixty two (51.2%) patients had body mass index (BMI) from 18.5-24.9 and 53 (43.8%) had BMI < 18.5, and only 6 (5.0%) had BMI ranges from 25-29.9.mean BMI was 18.33 ±3.87 kg /m^2.

Table (1): Distribution of the sample of children (121) according to different variables

Variables	Frequency	Percent
Age\ years		
< 10.0	62	51.2
10.0 –19.9	45	37.2
20.0 – 29.9	14	11.6
Mean = 10.44 ± 6.35		
Age \years on diagnosis		
< 1.0		
1.0 –1.99	77	63.6
2.0 – 2.99	22	18.2
3.0 –4.99	10	8.3
4.99- 9.99	6	5.0
10 –14.99	5	4.1
Mean ± 1.61	1	0.8
Sex		
Male	82	67.8
Female	39	32.2
Address		
Baghdad	85	70.2
Wassit	11	9.1
Karkuk	1	0.8
Diala	16	13.2
Karballa	4	3.3
Najaf	1	0.8
Salah - Aldeen	2	1.7
Babil	1	0.8
Residency		
Urban	78	64.5
Rural	43	35.5
Blood group		
A	36	29.8
B	36	29.8
AB	13	10.7
O	36	29.8
Rh factors		
+ve	110	90.9
- ve	11	9.1
Freq blood transfusion		
< 2 weeks	-----	--------
2 -4 weeks	85	70.2
> 4 weeks	36	29.8
Hemoglobin g\100 ml		
< 7.0	5	4.1
7.0 – 7.99	32	26.4
8.0 -10.0	81	66.9
> 10.0	3	2.6
Mean = 8.4 ± 1.12		
Body mass index (BMI)		
< 18.5	53	43.8
18.5 -24.9	62	51.2
25 – 29.9	6	5.0
Mean ± 3.87		
Freq desferol therapy		
< 3 times \ week	7	5.8
3 -4 times \ week	39	32.2
> 4 times \ week	75	62.0

Table (2) showed that there was significant difference between age of patient and frequency of blood transfusion (χ 2= 14.45 P= 0.01), age on diagnosis (χ 2=13.24 P= 0.03), residency and DFO therapy (χ 2= 4.99 P= 0.05).

Table (3) showed significant relation between age of patients and treatment schedule with DFO (χ2=13.38 P=0.001) and treatment with vitamin C (χ2=14.6 P=0.000). Table (4) showed that the mean serum levels of trace element, minerals and albumin in the sample were significantly different from the normal values for copper (t=4.04 P <0.001), zinc (t= -616.7 P < 0.001), selenium (t=8.22 P <0.001), calcium (t= 28.04 P <0.001), magnesium (t= -53.68 P<0.001), iron (t= -17.60 P<0.001), TIBC (t= -16.60 P<0.001) and albumin (t= -4.65 P<0.001).

There was significant correlation of serum zinc with vitamin C therapy, also magnesium correlated significantly with frequency of blood transfusion & DFO therapy. Serum iron correlated significantly with DFO therapy. Folic acid therapy correlated significantly with serum albumin and TIBC table(5).

Table (2): The relationship between the percentage of children (121) in the sample according to different variables and treatment schedules, body mass index

Variables	Blood transfusion			DFO *therapy \ weeks		
	<2weeks	2-4 weeks	> 4 weeks	< 3 times	3- 4times	> 4 times
Age\ years						
< 10.0	------	54.8	45.2	9.7	30.6	59.7
10.0 –19.9 20.0 –		86.7	13.3	2.2	37.8	60.0
29.9		85.7	14.3	----	21.4	38.6
Significant	χ^2=14.45	DF= 2	P= 0.01	χ^2= 5.12	DF= 4	P= 0.13
Age \year on Dx.						
< 1.0						
1.0–1.99	68.2	70.1	29.9	3.9	35.1	61.0
2.0– 2.99	70.0	31.8	-----	9.1	22.7	68.2
3.0–4.99	50.0	30.0		10.0	40.0	50.0
5.0 – 9.99	100.0	50.0		20.0	33.3	66.7
10 –14.99	100.0	------			20.0	60.0
					------	1
Significant	χ^2= 3.8	DF= 5	P= 0.57	χ^2= 5.54	DF= 10	P= 0.82
Sex						
Male	-----	69.5	30.5	6.1	32.9	61.0
Female		71.8	28.2	5.1	30.8	64.1
Significant	χ^2= 0.66	DF= 1	P= 0.49	χ^2= 0.12	DF= 2	P= 0.73
Residency						
Urban	-----	70.5	29.5	5.1	25.6	69.2
Rural	------	69.8	30.2	7.0	44.2	48.8
Significant	χ^2= 0.007 DF = 1 P = 0.55			χ^2= 4.99 DF= 2 P= 0.05		

*DFO= Desferrioxamine

Table (3): Show the association of some demographic features with the treatment schedules of the patients

Variables	DFO *therapy		Regularity of desferol		Folic acid therapy		Vitamine C therapy	
	Yes	No	Yes	No	Yes	No	Yes	No
Age\ years								
<10.0	47	15	34	13	60	2	46	16
10.0-19.9	44	1	29	15	44	1	44	1
20.0-29.9	14	----	12	2	14	-----	14	---
significant	χ^2= 13.38 DF=2 P=0.001		χ^2= 2.1 DF=2 P= 0.63		χ^2= 0.51 DF=2 P=0.50		χ^2= 14.6 DF=2 P=0.000	
Age\ years diagnosis								
< 1.0	67	10	46	21	74	3	67	10
1.0-1.99	20	2	16	4	22	-----	19	3
2.0-2.99	8	2	6	2	10		7	3
3.0-4.99	6	2	3	3	6		6	1
5.0-9.99	3	----	3	----	5		4	-----
10.0-14.99	1		1		1		1	
significant	χ^2= 4.92 DF=5 P=0.52		χ^2= 3.97 DF=5 P=0.53		χ^2=1.76 DF=5 P=0.29		χ^2=3.47 DF=5 P=0.81	
Sex								
Male	73	9	50	23	79	3	70	12
female	32	7	25	7	39	-----	34	5
significant								
	χ^2=1.12 DF=1 P=0.22		χ^2=1.01 DF=1 P=0.22		χ^2=1.46 DF=1 P=0.31		χ^2=0.07 DF=1 P=0.51	
Residency								
Urban	71	7	53	18	75	3	68	10
Rural	34	9	22	12	43	----	36	7
significant	χ^2=3.45 DF=1 P=0.06		χ^2=1.11 DF=1 P=0.20		χ^2=1.7 DF=1 P=0.26		χ^2=0.28 DF=1 P=0.4	

*DFO = Desferrioxamine

Table (4): Shows the different serum levels of trace elements, minerals and albumin in the sample of 121 patients

Variables	Mean	SE*	SD**	Minimum	Maximum	Normal value	T-test	P value
Copper µmol\L No=121 ***Dil factor=0	20.341	0.576	6.336	8.63	39.80	18	4.06	< 0.001
Zinc µmol\L No=121 Dil factor=10	0.816	0.023	0.253	0.27	1.30	15	- 616.7	< 0.001
Selinum µmol\L No=121 Dil factor=0	1.691	.0805	O.943	0.1	3.74	0.995	8.22	< 0.001
Calicium µmol\L No=121 Dil factor=0.7	0.329	0.027	0.304	0.01	1.94	2.6	-28.04	< 0.001
Magnesium µmol\L No=121 Dil factor=2	0.492	0.0076	0.083	0.20	0.73	0.9	- 53.68	< 0.001
Iron µmol\L No=112 Dil factor=5	13.070	0.496	5.250	6.21	30.26	21.8	-17.60	< 0.001
TIBC** **µmol\L No=112 Dil factor=2**	43.649	1.045	11.057	20.79	77.31	61.0	- 16.60	< 0.001
Albumin µmol\L No=121 Dil factor=0	4.163	0.073	0.798	0.38	6.10	4.5	- 4.65	< 0.001

***= Standard error**
****= Standard deviation**
*****= Dilution factor**
******= Total iron binding capacity**

Table (5): show the correlation between different blood levels of trace element and treatment schedules in the sample patients

Variables	Freq. blood transfusion	Desferol therapy	Reg. desferol therapy	Feq.desferol therapy	Vit. C therapy	Folic acid therapy
Copper						
P.Correlation	.013	.034	.079	-.047	.063	-.033
Significant	.443	.356	.194	.303	.247	.358
Number	121	121	121	121	121	121
Zinc						
P. Correlation	-.054	-.115	-.001	.094	-.152*	-.018
Significant	.280	.105	.497	.152	.048	.424
Number	121	121	121	121	121	121
Selenium						
P. Correlation	-.068	.077	.027	.032	-.083	-.063
Significant	.231	.201	.386	.365	.182	.245
Number	121	121	121	121	121	121
Calcium						
P. Correlation	.023	.020	-.083	.062	.054	-.008
Significant	.403	.412	.183	.250	.277	.467
Number	121	121	121	121	121	121
Magnesium						
P. Correlation	-.207*	-.152*	-.041	.125	-.082	-.139
Significant	.011	.049	.328	.085	.184	.065
Number	121	121	121	121	121	121
Albumin						
P. Correlation	.076	-.003	.046	-.041	.097	.195*
Significant	.203	.486	.307	.327	.145	.016
Number	121	121	121	121	121	121
Iron						
P. Correlation	-.069	.015	.056	-.160*	.044	.135
Significant	.235	.440	.279	.046	.322	.078
Number	112	112	112	112	112	112
TIBC						
P. Correlation	-.027	.010	.028	-.110	.022	.272**
Significant	.388	.458	.386	.124	.411	.002
Number	112	112	112	112	112	112

*= Significant at 0.05, **=Significant at 0.001

Discussion

In Iraq, Thalassemia major is an important public health problem. This is because of the considerable burden on the children and their families as well as on health services[15]. From the data of this study the mean age of diagnosis was 1.2 ±1.6 years and the mean patient age was 10.44 ± 6.35 years, this result agreed with the result obtained by Widad et al[15], in a study done by Zurlo etal [16], they found that the over all survival from birth for patients born in 1970-74 was 97.4% at 10 years and 94.4% at 15 years, the most common cause of death was heart disease, followed by infection, liver disease and malignancy. Modell M 2000[17] showed that patients who adhere fully to treatment usually complete their education, work, and find a partner, and are expected to live at least until their mid- forties.

In the past decade, treatment of patients with β-Thalassemia has changed considerably, with advances in red cell transfusion and the introduction of iron chelation therapy. This progress has greatly increased the probability for a Thalassemic child to reach adult age with a good quality of life[18]. While others[19, 20] stated that although treatment of patients with Thalassemia major has improved dramatically during the past 40 years, the current status of these patients remains poorly characterized. Currently all newborns in the United States are screened for hemoglobinopathies, if a newborn screen returns with large amounts of fetal hemoglobin, alpha hemoglobin, or hemoglobin

E, further investigation for Thalassemia takes place[21].

In the present sample male patients (67.8%) constituted higher number than females (32.2%), this could be explained by the fact that people especially in developing countries are more concern about their male children than female children. Pignatti et al[22] studied survival and complications in thalassemia major patients and found that females have a significantly better survival than males, both for the whole group born between 1960-1974 (P= 0.0242) and for the older patients (1960-1969) alone (P= 0.039). The mean Hb. level in the present sample was 8.4± 1.12 g\dl, this result is expected since those blood samples were taken from patients who were coming for blood transfusion and accordingly their Hb. level were expected to be low, it is higher than the result obtained by Widad et al [15].

As for treatment, it was found that most frequent blood transfusion was 2-4 weeks (which were significantly related to patients age) and DFO treatment > 4 times / week (which were significantly related to patients residency only).

BMI was significantly affected by age of the patient, it showed that around half of the patients were underweight which means that a good number of patient were suffering from growth retardation, probably those patients are in need of more aggressive treatment than the present one. In this study DFO therapy have a significant and inverse correlation with height and weight of patients, the association was also found when height and weight of patients were studied with the frequency of DFO therapy, this result agreed with the study done by Pooya et al 2004 [23] they suggested that it is essential to determine a safe dose for using deferoxamine in thalassemic patients not only for effective iron chelation and preventing haemochromatosis but also for decreasing its side effects such as growth retardation. Growth failure had been attributed to; chronic anemia, zinc deficiency, growth hormone deficiency, secondary to deferoxamine therapy and many other causes[24]. Some studies have shown that nutrition intervention might result in a significant improvement in mean weight for height with increase in zinc plasma levels and a decrease in plasma copper levels[25]. Other clinical trials showed that treatment with zinc supplementation and / or growth hormone may enhance growth velocity and may manage growth retardation of the treated group[26, 27].

The mean levels of trace elements, minerals, and albumin were significantly lower among the sample of thalassemic patients except for serum copper which was significantly higher than normal mean level. `The finding of high serum copper is with agreement with other studies in different parts of the world [15, 28, 29], while it disagree with the result obtained by Nasr 2002[30]. The result of low serum zinc is with agreement with many other studies[15, 30, 31, 32]. These finding could be explained by the antagonistic effect of the zinc, as zinc deficiency in β- Thalassemia major could greatly increase copper absorption via the gastrointestinal tract[33]. Serum zinc level shows negative (not significant) correlation with treatment and regularity of treatment of DFO, this result coincide with many other studies[31, 32, 34], it could be explained by the fact that DFO therapy is associated with increase urinary zinc excretion in β-thalassemia major as desferrioxamine could have an affinity to other metal ions including zinc[34, 35], also in this study it was found that regularity of treatment with DFO is negatively correlated with calcium and magnesium level in the thalassemic major patients, while DFO therapy negatively correlated with magnesium (significant association) and albumin level in blood. Frequency of blood transfusion was negatively correlated with magnesium level (significant association), zinc, selenium, iron and TIBC, this could be explained partly due to the effect of other treatment schedules given to thalassemic patients. Follate therapy showed negative correlation with serum copper, zinc, selenium, calcium, magnesium and significant positive correlation with albumin & TIBC, Milne et al[28] studied the effect of follate supplementation on some trace elements absorption and excretion and concluded that supplementation of follate influence zinc homeostasis, perhaps through formation of an insoluble chelate and impairment of absorption. This could add another factor responsible for zinc deficiency in patients with β-thalassemia major as most of those patients take follate therapy continuously.

The low level of iron & TIBC could be partly due to the fact that most of our patients take ascorbic acid (vitamin C) therapy, ascorbic acid facilitates the release of iron from the storage sites, as well as it can also increase its utilization by the erythroid cell and increase iron excretion by the kidney in the presence of desferrioxamine[36]. Vitamin C in the present study also shows negative correlation with zinc (significant association), selenium, and magnesium blood levels among the thalassemic patients.

Conclusion and recommendation: The study shows that majority of patients were of young age groups < 20 years of age with large proportion of them suffering from growth retardation, anemia and abnormally low blood level of some trace element and minerals suggesting the possibility of inaccurate treatment schedules. The following are recommended:

A- It is very important that more centers for thalassemia are to be established in different areas in our country, with increase efficiency for treatment and follow up of patients

B- To establish centers that tried newer therapy like stem cell transplantation.

C-To established programs based on carrier screening and counseling of couples at marriage, preconception or early pregnancy, which can be done by simple hematological analysis. These programs are operating in several Mediterranean at risk population, and are very effective, as indicated by increasing knowledge on thalassemia and its prevention by the target population and by the marked decline of the incidence of thalassemia major.

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