ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

B-thalassemia intermedia in Babylon Thalassemic centre Babil, Iraq.

Jasim M. Al-Marzoki*, and Zainab W Al-Maaroof Sura M Abes.

Department of Pediatrics, Department of Hematology, Babylon university- Medical Faculty, Iraq.

ABSTRACT

Thalassemia intermedia is a term used to define a group of patients with β thalassemia in whom the clinical severity of the disease is somewhere between the mild symptoms of the β thalassemia trait and the severe manifestations of β thalassemia major. This study was done to determine the demographic; clinical, laboratory data and management of patients with thalassemia intermedia. A retrospective study done in Babylon center for thalassemia in Babylon Maternity and Children Hospital. Seventy patients diagnosed as thalassemia intermedia were enrolled in our study, with patient's age (1-18)years during a period from (July 2014-June 2016). Data were collected including : history, clinical manifestation , physical examination and management. There was no significant relation between the current age ,age at diagnosis, and duration of the disease in relation to gender, p values were (0.155,0.216,0.555) respectively. Height and weight percentile median 10 and IQR (10-25),median 10 and IQR 5-25 respectively. The mean and SD. for age at first blood transfusion were 8.1±2.6 years respectively. Serum ferritin was independent predictor of blood transfusion. Many patients with thalassemia intermedia need no blood transfusion while some patients need frequent blood transfusion. longer duration of disease, advanced current age, and higher serum ferritin level all were associated significantly with more need for blood transfusion.

Keywords: Thalassemia intermedia, Babylon, Ferritin, blood transfusion

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Thalassemia is a well-known autosomal recessive inherited hematologic disorder caused by a decrease or an absence of globin chain production. [1] Thalassemia intermedia [TI] was illustrated in 1955 by Rietti- Greppi-Micheli, who described patients as being too haematologically severe to be called minor, but too mild to be called major. [2] The terminology has been changed from TI to NTDT[non-transfusion dependent thalassemia. [3] Generally patients with NTDT can maintain hemoglobin levels at 6–10 g/dL with occasional need for blood transfusions that may be required with fever, infection, or pregnancy. [4, 5, 6,7] Most patients with this disorder are homozygotes or compound heterozygotes [8] Less commonly, only a single beta-globin locus is affected, and the other being completely normal. [9] Thalassemia intermedia present more commonly in the Mediterranean basin, northern Africa, the Indian subcontinent, and Eastern Europe than in other areas of the world. [10] Main clinical features that may be present in patients with thalassemia intermedia are hypertrophy of erythroid marrow with medullary and extramedullary hematopoiesis with its associated complications and gallstones.[11] Iron overload in non-transfused patients is due to augmented gastrointestinal absorption and involves mainly the liver. [12] The hepatic peptide hepcidin normally regulated by marrow activity and by iron load, is disproportionately low in patients with thalassemia, allowing iron to be absorbed from the gut even in the presence of severe overload. [13] Although individuals with thalassemia intermedia are at risk of iron overload, hypogonadism, hypothyroidism and diabetes are not common. [14] Hemolysis carries a role in the dysregulation of nitric oxide (NO) homeostasis which is correlated with pulmonary hypertention and probably thrombotic phenomena. [15] These events include deep vein thrombosis, portal vein thrombosis, stroke and pulmonary embolism. [16] Patients with beta thalassemia intermedia, have decreased total cholesterol and LDL-cholesterol, the mechanisms that may account for these findings are increased erythropoiesis and cholesterol consumption in beta thalassemia intermedia. [17] Patients with thalassemia intermedia who do not have severe hemosiderosis are less prone to cardiac problems. [20] There are no clear guidelines for managing patients with thalassemia intermedia. Although earlier introduction of blood transfusions will increase the rate of iron accumulation, effective methods of iron chelation are now available. [17, 19]

Sometimes transfusion becomes necessary during infection-induced aplastic crises, heart disease and leg ulcer are also an indication for transfusion therapy. [17] The current indications for splenectomy in TI include growth retardation and hypersplenism. [4] Overwhelming sepsis that occures postsplenectomy is an abrupt event that can be fatal, the most frequent bacteria are Streptococcus pneumonia , Hemophilus influenzae, Neisseria meningitidis, Klebsiella, Escherichia coli and Staphylococcus aureus. [17] Iron-loaded macrophages lose its ability to kill intracellular pathogens via the interferon-γ-mediated pathways, some of this loss of ability is related to the reduced formation of nitric oxide in the presence of iron. [20] If gallstones are present, cholecystectomy should also be performed at the same time of splenectomy.[17] A direct assessment of liver iron concentration is recommended, either by biopsy or by MRI which is non invasive method. Chelation therapy should generally be initiated if liver iron concentration exceeds 7 mg/g dry weight of liver tissue. Serum ferritin values of 400–500 ng/ml could be considered as an indicator for initiation of iron chelation therapy. [21] The orally chelators seem to be more efficient in gaining access to the chelatable iron pools of cardiomyocytes, binding labile iron, and attenuating reactive oxygen species formation. [22] Hydroxycarbamide: also known as hydroxyurea is capable of inducing HbF synthesis and stimulating γ-globin production, it may have a more general role in augmenting globin synthesis, including β-globin in some thalassemia intermedia patients who maintain the capacity to express normal β-globin. [23] A significant decrease in the need for blood transfusions was observed in many patients; it may be completely obviated in some patients. [24]Trials of recombinant human erythropoietin (rHuEPO) for the treatment of thalassemia showed a significant, increase in thalassemic erythropoiesis. [25] Because folic acid deficiency is common in TI and occurs due to poor absorption, low dietary intake, or due to increase demand for folic acid from active bone marrow with increased erythropoiesis. [6.17] Daily supplementation with 1 mg of folic acid is advised for patients with thalassemia intermedia. [26] Zinc supplements may become necessary during intense chelation which decrease oxidetive stress and reduce incidence of infections. [6] Hematopoietic stem cell transplantation has rarely been used in patients with thalassemia intermedia. [6]Molecular therapies with transfer of a globin gene in autologous haematopoietic stem cells poses challenges in terms of controlling transgene expression, which should be erythroid-specific, differentiation- and stage-restricted, position independent and sustained over time. [27] Patients with mild disease of thalassemia intermedia have a good prognosis; however after several years of stable disease, many patients develop the severe form of the condition and become transfusion dependent. Patients with severe forms have the same prognosis as those patient with thalassemia

major. In most cases, the transformation from the stable state to the transfusion-dependent state is gradual. [28] This study was done to determine the demographic; clinical, laboratory data and management of patients with thalassemia intermedia.

PATIENTS AND METHODS

A retrospective study conducted in Babylon Maternity and Children Hospital (Thalassemia center) Babil/IRAQ from July 2014 to June 2016 on records of patients with thalassemia intermedia diagnosed by Hb electrophoresis. Data were collected from 70 patients including: history (the current age, age at diagnosis , age at first blood transfusion, number of blood transfusion in the last year, family history of thalassemia), regarding physical examination(growth parameters, hepatomegaly, splenomegaly, and thalassemic face), concerning investigations(serum ferritin, alanine transferase, thyroid stimulating hormone, thyroxin , fasting blood sugar, white blood cell, hematocrite level, red blood cell count, red blood cell distribution width , mean corpuscular volume, mean corpuscular hematocrit, mean corpuscular hematocrit concentration, and platelets), regarding management (use of hydroxyuria, chelating therapy).

Statistical analysis:

All data analyzed using SPSS version 20 software package and minitab version 17, p value was considered to be significant if < 0.05.The data presented using the mean and standard deviation (if it follow normal distribution), but if it did not follow normal distribution the median and interquartile range used. Independent t-test used to analyze the difference in means between 2 groups, logistic regression analysis association between predictors data presented using their odd ratio and its 95% confidence interval.

RESULTS

This study included 70 patients diagnosed as thalassemia intermedia who attended Babylon Thalassemia Center of Babylon Maternity and Children Hospital. The studied patients were 36 (51.4%) females and 34 (48.6) males with male to female ratio of 0.9:1.The current age in years was ranging between (4-18)with mean and SD. 10.9 ± 3.6 as shown in table (1). The age at diagnosis in years was ranging between (1-12) with mean and SD. 5.54± 2.59, duration of the disease in years was ranging between (2-11)with mean and SD. 5.44± 3.23 , the mean and SD. Of age of starting chelating therapy were 13.5±1.4 year as seen in table (1). There was no significant relation between the current age ,age at diagnosis, and duration of the disease in relation to gender, p values were (0.155,0.216,0.555) respectively as illustrated in table (2). Height and weight percentile median 10 and IQR (10-25),median 10 and IQR 5-25 respectively as seen in table (1). There was 8 (11.4%) patients developed short stature where height percentile was below 5th centile and 10 (14.2%) patients developed low body weight in which weight percentile was below 5th centile. The mean and SD. for age at first blood transfusion were 8.1±2.6 years respectively, thalassemic face was present in 14 (20%) of patients . About laboratory analysis regarding a mean and SD :for WBC were (8.34±2.60), for PCV were(28.44±2.70), for platelets were (266.9±102,36), for MCV were (71.15±8.7), for MCH were (27.6±3.6), for MCHC were (30.8±3.1), for RDW were (29.1±4.04), for RBC were (2.67±0.78), for s.ferritin were (482.6±250.7), for ALT were (10.5±4.2), for TSH (3.08±1.05), for T4 (81.33±12.42), for FBS were (80.07±11.86). In our stuy only s.ferritin was independent predictor of blood transfusion, p value (0.002) . Regarding chelating therapy(exjade, desferoxamine) was used in 15.7% of patients. Figure (1) demonstrate that 38 patient had no need for blood transfusion, 21 patient need 1 time blood transfusion, 2 patient need 2 times blood transfusion, 1 patient need 3 times blood transfusion, 4 patients need 4 times blood transfusion, and 4 patients need 5 times or more blood transfusion.Table (6) demonstrates that increased number of blood transfusions, longer duration in years for blood transfusion, longer duration of the disease, and higher current age all these parameters associated significantly with developing splenomegaly . Advanced age at first blood transfusion, and advanced age at diagnosis associated weakly with increase odd for having splenomegaly. Height , weight and gender not significantly associated with splenomegaly . Table (7) demonstrates higher number of blood transfusion, longer duration of disease, longer duration of blood transfusion, and advance current age all these factors associated strongly and significantly with hepatomegaly. Gender and advanced age at first transfusion associated weakly with increase odd for having hepatomegaly. Weight, height and advanced age at diagnosis not significantly associated with developing hepatomegaly . Table (8) shows longer duration of disease, advance current age and higher ferritin level all associated significantly with more need for blood transfusion (strong predictors) in univariate analysis. In multivariate analysis only serum ferritin was

ISSN: 0975-8585

independent predictor of blood transfusion and the other predictors were not significant so we referred to it as (-).

Table 1: Demographic data of patients with thalassemia intermedia			
	Range	Mean	SD
Current age (years)	4 - 18	10.98	3.61
Age at Dx (years)	1 - 12	5.54	2.59
Duration of disease (years)	2 - 11	5.44	3.23
Height percentile (median, IQR)	10 (10 – 25)		
Weight percentile (median, IQR)	10 (5 – 25)		

Table 2: Demographic data divided by gender of patients with thalassemia intermedia						
	Range	Female		Male		P value
		Mean	St. dev.	Mean	SD	
Currant age (years)	4 - 18	11.58	3.51	10.35	3.65	0.155
Age at diagnosis (years)	1 - 12	5.92	2.73	5.15	2.40	0.216
Duration of disease (years)	2 - 11	5.67	3.11	5.21	2.39	0.555

Table 3: Organ involvement of patients with thalassemia intermedia		
	No	%
Splenomegaly	43	61.4%
Size of spleen (cm)	3.09 ± 1.29	
Hepatomegaly	25	35.7%
Size of liver (cm)	2.6 ± 0.6	

Table 4: Mode of therapy for patients with thalassemia intermedia		
Therapy mode	No	%
Chelating therapy	11	15.7%
Hydroxy urea	10	14.3%
No therapy	49	70%

Table 5: Laboratory analysis of patients with thalassemia intermedia			
Laboratory parameters	Range	Mean	St. Dev.
WBC-10^3/uL	5.2-16.5	8.34	2.60
PCV %	23.4-34	28.44	2.70
Platelates10^3/uL	155-470	266.93	102.36
MCV fL	53.5-88.7	71.15	8.72
MCH pg	19.8-34.5	27.69	3.62
MCHC g/dl	24.6-39.6	30.84	3.18
RDW %	20.8-36.5	29.13	4.04
RBC-10^6/uL	1.7-4.4	2.67	0.78
S. Ferritin ng/ml	190-2100	482.63	250.77
ALT U/L	5-20	10.56	4.22
T4 nmol/L	62.6-110	81.33	12.42
TSH uIU/ml	1.5-5.1	3.08	1.05
FBS mg/ dl	60-100	80.07	11.86

Table 6: Predictors of splenomegaly of patients with thalassemia intermedia			
Variables	OR	95% CI	P value
Number of blood transfusion	6.899	2.046 – 23.267	0.002
Duration of blood transfusion (years)	1.571	1.139 – 2.167	0.006
Duration of disease (years)	1.561	1.229 – 1.984	<0.001
Current age (years)	1.493	1.227 – 1.816	<0.001
Age at first transfusion (years)	1.241	0.992 – 1.552	0.058
Age at diagnosis (years)	1.116	0.919 – 1.355	0.268
Height percentile	0.979	0.951 – 1.008	0.154
Weight percentile	0.972	0.942 – 1.003	0.077
Gender	0.495	0.186 – 1.316	0.159

ISSN: 0975-8585

Table 7: predictors of hepatomegaly of patients with thalassemia intermedia			
Variables	OR	95% CI	P value
Number of blood transfusion	2.09	1.295 – 3.373	0.003
Gender	1.591	0.584 – 4.258	0.355
Duration of disease (years)	1.419	1.178 – 1.708	<0.001
Duration of blood transfusion (years)	1.339	1.059 – 1.693	0.015
Current age (years)	1.278	1.084 – 1.506	0.004
Age at first transfusion (years)	1.023	0.838 – 1.249	0.823
Height percentile	0.992	0.962 – 1.022	0.581
Weight percentile	0.988	0.967 – 1.030	0.895
Age at diagnosis (years)	0.93	0.766 – 1.129	0.463

Table 8: predictors of blood transfusion of patients with thalassemia intermedia						
Variables	OR	95% CI	P value	OR	95% CI	P value
	Univariate			Multivariate		
Gender	0.700	0.272 – 1.801	0.460	-	-	-
Duration of disease (years)	1.298	1.097 – 1.537	0.002	-	-	-
Current age (years)	1.254	1.076 – 1.462	0.004	-	-	-
Height percentile	1.006	0.978 – 1.034	0.691	-	-	-
Weight percentile	0.975	0.944 – 1.007	0.125	-	-	-
Age at diagnosis (years)	1.023	0.852 – 1.229	0.806	-	-	-
Fx of thalassemia	2.571	0.439 – 15.063	0.295	-	-	-
Age at 1st blood transfusion	1.11	0.909 – 1.359	0.308	-	-	-
MCV	0.972	0.920 – 1.028	0.318	-	-	-
RDW	1.025	0.912 – 1.153	0.676	-	-	-
RBC	0.643	0.344 – 1.201	0.166	-	-	-
MCHC	1.055	0.905 – 1.228	0.495	-	-	-
PCV	0.828	0.684 – 1.002	0.052	-	-	-
MCH	0.885	0.769 – 1.018	0.088	-	-	-
S. Ferritin	1.004	1.002 – 1.007	0.002	1.003	1.000 – 1.005	0.039

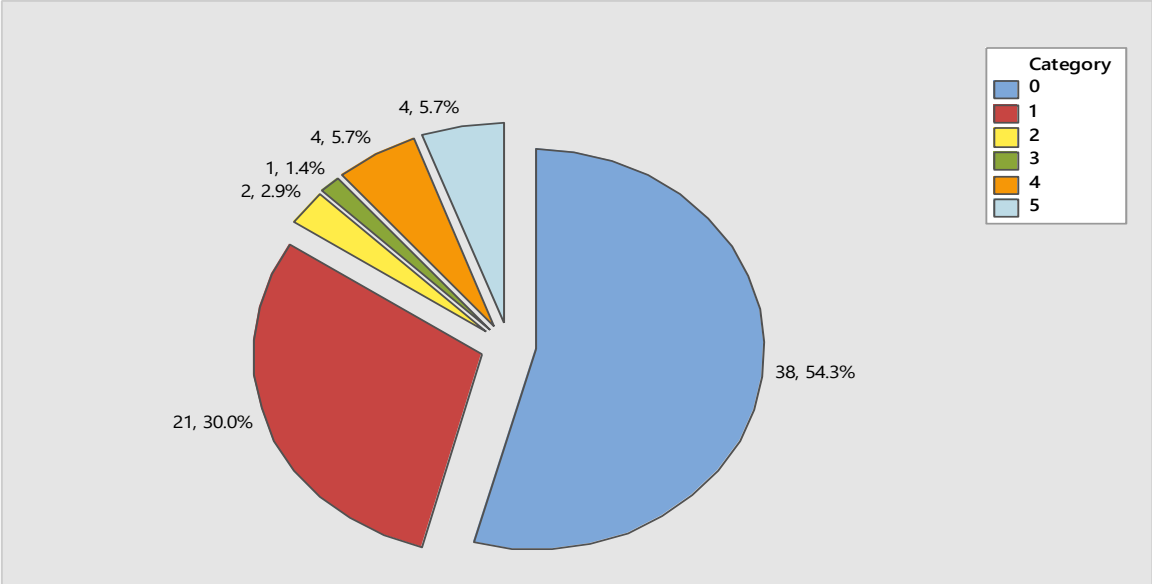

Figure 1: Pie chart of the frequency of blood transfusion

ISSN: 0975-8585

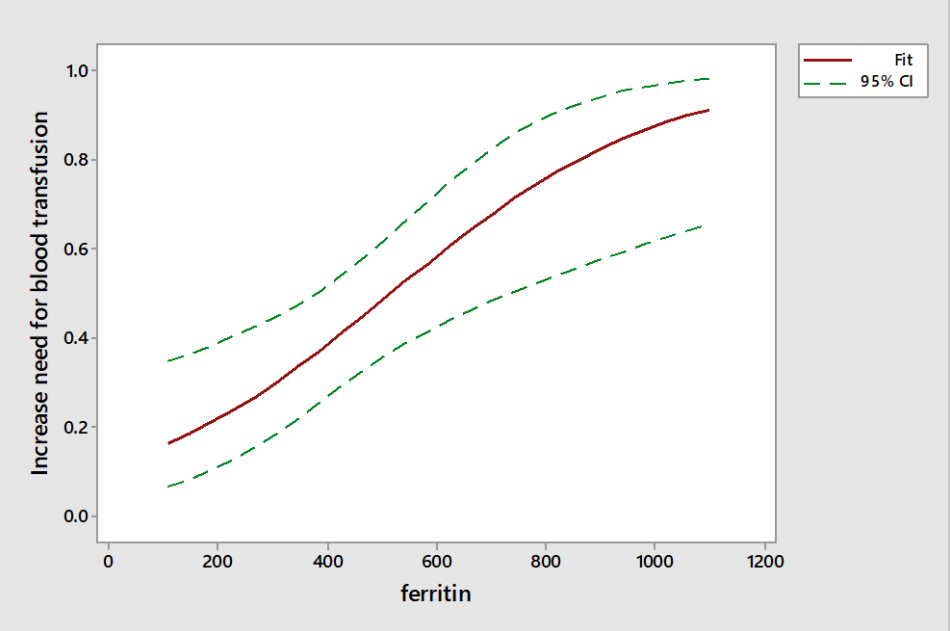

Figure 2: Probability plot of increase need for blood transfusion with high S. ferritin

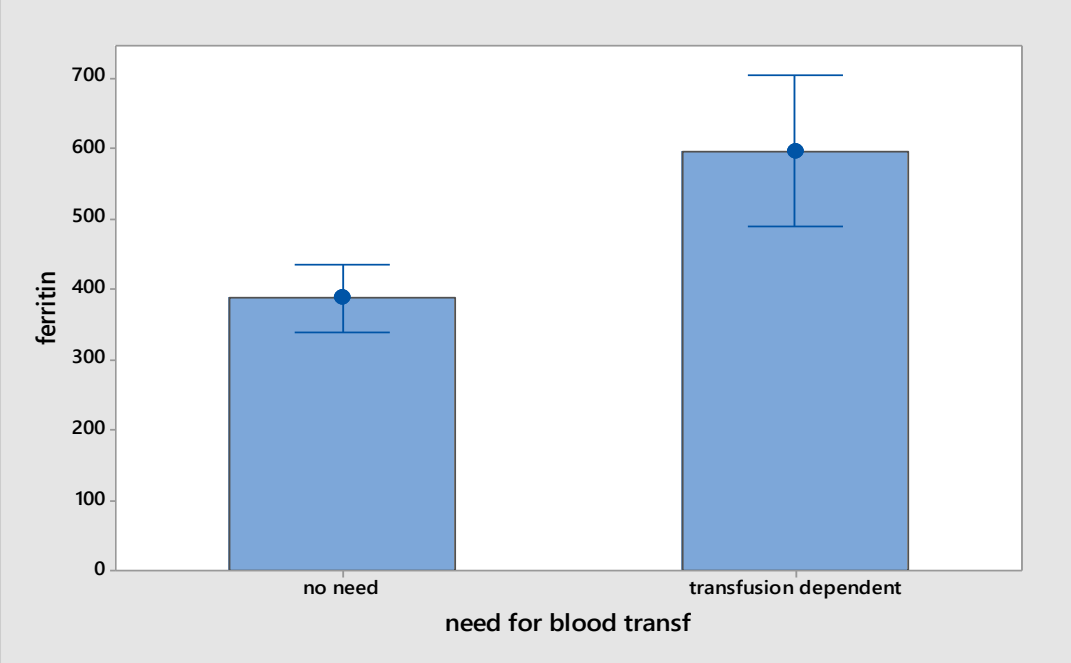

Figure 3: Serum ferritin relation for blood transfusion

DISCUSSION

In our study we enrolled 70 patients with mean age and SD. of 10.98±3.6 years . The mean and SD. for age at diagnosis were 5.5±2.5 years, and the gender distribution was the females No.36 (51.4%), the males No. 34(48.6%), this is close to a study carried out in North India [29] in which mean age and SD. were 10.9±5 years. The mean and SD. for age at diagnosis were 4.2±2.3 years, and the gender distribution was equal among the groups. In current study, the number of patients with no history of blood transfusion was (38) 54.3%, this goes with a study done in hematology clinic of Cairo University Children Hospital from 2003-2006 [30] in which No. Of patients with no history of blood transfusion was(30) 51.7%, while it is not goes with our study regarding No. Of patients with (1,2,3,4,5 or more) times of blood transfusion, because in our study, it was (30%,2.9%,1.4%,5.7%,5.7%) respectively ,while In Cairo study, the No. Of patients with (1,2,3,4 or more)

times of blood transfusion was (46.4%,14.3%,14.3%,25%) respectively. Seventy nine patients were enrolled in a study done in Northen Iraq [31] where 32.4% of them were never transfused so it is away from our study, this results may be due to the different age group enrolled in the studies. Regarding clinical findings in a study of Cairo University[30] splenomegaly was present in (70.2%) of patients, hepatomegaly in (67.2%) of patients , while in our study splenomegaly was present in (61.4%) of patients , and hepatomegaly was present in patients(35.7%) of patients , this results may be due to the difference between the total No. Of patients included in the studies. About thalassemic faces in our study, it was seen in(10%)of patients, while in a study done for patients with TI in Northen Iraq [31] thalassemic face was present in 54 (73%) patients . In concern to laboratory analysis in our study , WBC count mean and SD. were 8.3 ±2.6 which is close to a study in Cairo university[30] where the mean and SD. were 8.8 ±2.3 , but the other indices in form of (RBC, PCV, MCV, MCH, MCHC, and platelets) were away from our study the values were (2.6±o.78, 28.4±2.7,71.1±8.7, 27.6±3.6, 30.8±3.1, 266.9±102.3),while in Cairo study [30] the values were (3.5±0.8,21.6±4.9,60.2±10.7,20.2±4,33.1±4.4,409.8±225.9), the mean and SD. For MCV in a study was done in Northen Iraq [31] was 63±7.3 so it is not goes with our study. Regarding thyroid function in patients with TI in our study the mean and SD. for T4 and TSH were(81.3±12.4,3.08±1.05) respectively and no patient developed hypothyroidism which is close to a study done in southern Iran during 2010 [32]in which the mean and SD. of T4 and TSH were(83±11,2.7±1.7), this is explained by although individuals with thalassemia intermedia are at risk of iron overload, hypothyroidism was not common. The mean and SD. of S.ferritin in our study were (482.6±250.7)which is close to a study was done in North India on patients with TI [29] where the mean and SD. were (486.5±640). In a study of Northen Iraq S.ferritin mean and SD. were 927.6±999, so it is away from our study. in our study chelating therapy was used in 11(15.7%) patients, and hydroxyurea was used in 10(14.3%) patients, while in a study done in 6 comprehensive care centers in (Lebanon, Italy, Iran, Egypt, United Arab Emirates, and Oman) [33], chelating therapy was used in 336(47.5%) patients and hydroxyurea was used in 202(34.6%) . Considering FBS in our study the mean and SD. were 80.07 ± 11.8, this mean no patient developed DM, while in Ali T. Taher,et al study [33] 10 (1.7%) patients developed DM . Regarding liver function test in our study ALT mean and SD. were 10.5 ± 4.2, so the result was normal, while 57 (9.8)% patient developed abnormal LFT in Ali T.Taher ,et al study. [33]

CONCLUSION

Many patients with thalassemia intermedia need no blood transfusion while some patients need frequent blood transfusion. longer duration of disease, advanced current age, and higher S. ferritin level all were associated significantly with more need for blood transfusion.

REFERENCES

[1] Hoffman R. , Benz E. J. and Shattil S. S.. P. J. Giardina, “Thalassemia syndromes” in *Hematology: Basic Principles and Practice*, 5th edition, 2008.

[2] Taher A. ,Isma’eel H .,Cappellini MD.,Thalassemia intermedia:Revisited.Blood cell,Molecules and Disease ,12_20,2006.

[3] Weatherall D. J. , The definition and epidemiology of non transfusion-dependent thalassemia . *Blood Reviews*,vol (26) , 2012.

[4] Cappellini M.D , Musallam K.M. and Taher A. T .“Insight onto the pathophysiology and clinical complications of thalassemia intermedia.” *Hemoglobin*, vol. 33, supplement 1, pp.145–159, 2009.

[5] Rassi F. El, Cappellini M.D., Inati A., et al.“Beta-thalassemia intermedia: an overview”. *Pediatric Annals*, vol. 37, no. 5,pp. 322–328, 2008.

[6] Borgna-Pignatti C. Modern treatment of thalassaemia intermedia, Br J Haematol, 138 , pp. 291–304, 2007.

[7] Taher A. T. , Musallam K. M. , Karimi M., et al . “Overview on practices in thalassemia intermedia management aiming for lowering complication rates across a region of endemicity: the OPTIMAL CARE study” . *Blood*, vol. 115, no. 10, pp. 1886–1892, 2010.

[8] Galanello R. , Cao A. . Relationship between genotype and phenotype. Thalassemia intermedia, Sci. 850 , 325–333, 1998.

[9] Weatherall D. . The molecular basis for phenotypic variability of the common thalassaemias, Mol. Med. Today 1 15–20, 1995.

[10] Lilleyman JS, Hann IM, Blanchette V, eds: The thalassemias: *Pediatric Hematology*, 2nd ed.. 316, 325, 2000.

[11] Galanello Renzo, Origa Raffaella , Beta-thalassemia. Orphanet J Rare Dis, p. 5-11, 2010.
[12] Borgna-Pignatti C , Marsella M , Zanforlin N . The natural history of thalassemia intermedia. Ann N Y Acad Sci, 1202, pp. 214–220,2010.
[13] Kattamis A, Papassotiriou I , Palaiologou D , *et al.*The effects of erythropoietic activity and iron burden on hepcidin expression in patients with thalassemia major . Haematologica,91, pp. 809–812, 2006.
[14] De Sanctis c ,Tangerini A ,Testai M.R , *et al.* Final height and endocrine function in thalassemia intermedia. J Pediatr Endocrinol Metab,11, pp. 965–971,1998.
[15] Taher A. T , Musallam K. M and Cappellini M. D . "Thalassaemia intermedia: an update."Mediterranean Journal ofHematology and Infectious Diseases, vol. 1, no.1, 2009.
[16] Taher A.T,Otrock Z. K ,Uthman I ,et al. Thalassemia and hypercoagulability.Blood Rev, 22 , pp. 283–292,2008.
[17] Sezaneh H , Maryam D , Behrang S , et al. Serum lipid profiles in patients with beta-thalassemia major and intermedia in southern Iran. J Res Med Sci, 15 (3), pp. 150–154,2010.
[18] Aessopos A , Farmakis D , Karagiorga M , *et al.* Cardiac involvement in thalassemia intermedia: a multicenter study. Blood, 97 , pp. 3411–3416, 2001.
[19] Eder A.F, Chambers L.A . Noninfectious complications of blood transfusion. Arch Pathol Lab Med, 13, pp. 708–718,2007.
[20] Vento S , Cainelli F, Cesario F . Infections and thalassaemia. Lancet Infect Dis, 6, pp. 226–233,2006.
[21] Cappellini MD, Cohen A, Eleftheriou A, et al. Guidelines for the clinical management of thalassaemia, 2nd revised edition. Thalassaemia International Federation; 2008.
[22] Glickstein H , El RB, Link G. , *et al.* Action of chelators in iron loaded cardiac cells: accessibility to intracellular labile iron and functional consequences. Blood, 108, pp. 3195–3203,2006.
[23] Zeng Yi T. , Huang S.Z , Ren Z.R , *et al.*Hydroxyurea therapy in β-thalassemia intermedia: improvement in hematological parameters due to enhanced β-globin synthesis. Br J Haematol, 90, pp. 557–563,1995.
[24] Karimi M, Yarmohammadi H, Farjadian S, et al. Beta-thalassemia intermedia from southern Iran: IVS-II-1 (G –>A) is the prevalent thalassemia intermedia allele. Hemoglobin ; 26(2):147–54,2002.
[25] Bohl D , Bosch A, Cardona A ,et al. Improvement of erythropoiesis in beta-thalassemic mice by continuous erythropoietin delivery from muscle. Blood, 95, pp. 2793–2798,2000.
[26] Mojtahedzadeh, Kosaryan M , Mahdavi M.R , et al.The effect of folic acid supplementation in beta-thalassemia major: a randomized placebo-controlled clinical trial. Arch Iranian Med, 9 , pp. 266–268,2006.
[27] Sadelain M . Recent advances in globin gene transfer for the treatment of beta-thalassemia and sickle cells anemia. Curr Opin Hematol, 13, pp. 142–148, 2006.
[28] Rund D, Rachmilewitz E . Beta-thalassemia. N Engl J Med; 353:1135,2005.
[29] Ravi Shah, Amita Trehan, Reena Das , et al.Serum Ferritin In Thalassemia Intermedia, Indian J Hematol Blood Transfus. 30(4):281-285, 2014.
[30] Nermeen Kaddah, Khaled Salama, Epidemiological Study among Thalassemia Intermedia, Med.J.Cairo Univ.,Vol.78, No. 2, December 651-655,2010.
[31] Nasir A. S. Al –Allawi, Sana D. Jalal,Ameen M. Mohammad, et al.B-Thalassemia intermedia in Northen Iraq, Hindawi Publishing Corporation BioMed Research International, 2014.
[32] Omid Reza Zekavat, Ali RezaMakarem, Sezaneh Haghpanah, et al. Hypothyroidism in B-thalassemia intermedia, IJMS Vol 39, No 1,January 2014.
[33] Ali T. Taher, Khaled M.Musallam, Mehran Karimi, et al.Overview on practices in thalassemia intermedia management aiming for lowering complication rates across a region of endemicity.blood journal, 2015.