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Hematologic profiles of Beta thalassemia major patients: An institutional cross-sectional study

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Abstract

Introduction: Thalassemia is inherited blood disorder characterized by decreased hemoglobin with two main types-alpha and beta thalassemia. There are two main varieties of β thalassaemia, β0 thalassaemia, in which no β globin is produced, and β+ thalassaemia, in which some β globin is produced, but less than normal. As the patient is diagnosed, regular blood transfusions and chelating treatment is given lifelong. In this study, we observed the haematological profiles of multi transfused thalassemia major patients with the accompanying complications.

Aims and Objectives: To study the clinical features with RBC parameters, serum ferritin levels, chelation therapy and prevalence of blood transfusion related infection in multi transfused beta thalassemia major patients.

Materials and Method: In this cross sectional study, total 90 diagnosed thalassemia major patients were taken with their complete history, physical examination and laboratory parameters such as-complete blood counts. All the patients were monitored for serum ferritin levels and chelation therapy along with screening for transfusion transmitted infections over a year. All the data were compiled and appropriate statistical analysis was done.

Results: In present study out of 90 patients, 54 patients were males and 36 patients were females. Mean age of 15.26 ± 7.04 years with 68.9% (N=62) of cases required twice monthly transfusion, 30.0% (n=27) cases required once a month transfusion. 25 cases were found to be HCV+ (27.78%), 3 were HIV + (3.3%) and 62 cases were n on-reactive (68.89%). On first post transfusion CBC we found that 30 cases (33.33%) were found to be adequately transfused with levels > 10 gm%, where as in second results 34 cases (37.78%) were found to be adequately transfused with levels >10 gm%. Mean of average yearly average ferritin values in the study duration was found to be 4724 ± 287.65 ng/mL. The chelating agent dose was with mean 1040 mg and standard deviation 476.19.

Conclusion: In the present study, it is concluded that haematological parameters like Haematocrit, Red Blood Cell mass, Haemoglobin and Mean Corpuscular volume had large covariances and Serum Ferritin levels was positively correlated with chelation therapy along with increased rate of transfusion transmitted infections in multi transfused thalassemia major patients.

Keywords: Multiple blood transfusion, serum ferritin, chelation therapy, hemoglobinopathies

Introduction

Thalassemia is inherited blood disorders characterized by decreased haemoglobin production. There are two main types, alpha thalassemia and beta thalassemia. The severity of alpha and beta thalassemia depends on how many of the four genes for alpha globin or two genes for beta globin are missing [1, 2]. Thalassemia gene mutations occur most frequently in a broad geographic belt extending from the Mediterranean basin through the Middle East, Indian subcontinent, Burma, Southeast Asia, Melanesia, and the islands of the Pacific Ocean [3]. Certain communities in India, such as Sindhis and Punjabis from Northern India, Bhanushali's, Kutchis, Lohana's from Gujarat, Mahar's, Neobuddhist's, Koli's and Agri's from Maharashtra, & Gowda's and Lingayat's from Karnataka etc. have a higher carrier rate [4, 5].

There are two main varieties of β thalassaemia, β0 thalassaemia, in which no β globin is produced, and β+ thalassaemia, in which some β globin is produced, but less than normal. Less severe forms of β thalassaemia are sometimes designated β++ to indicate that the defect in β-chain production is particularly mild. The diagnostic feature of β thalassaemia is an elevated level of HbA2 in heterozygotes, which is found in most forms of β0 and β+ thalassaemia [6].

After the diagnosis of patient with thalassemia major, Management includes regular 3 weekly filtered packed red cell transfusions, chelation therapy for iron overload, management of complications of iron overload and transfusions, including osteoporosis, cardiac dysfunction, endocrine problems, Hepatitis B & C, HIV infection, CMV etc. [7].

In regularly transfused people, laboratory investigations, such as Complete Blood Count (CBC), reticulocyte counts, serum ferritin levels are monitored to know the effectiveness of transfusion. RBC indices and their comparison pre transfusion and post transfusion is also helpful in analysing overall health of patients and to predict associated comorbidities [8].

Aims and Objectives

- To study various RBC parameters and their correlations in multi- transfused beta thalassemia major patients.
- To assess changes of serum ferritin levels at subsequent blood transfusions and effectiveness of chelation therapy.
- Prevalence of seropositivity among beta thalassemia major patients.

Materials and Method

The study included total 90 patients with beta thalassemia major, from pediatric/medicine department in a tertiary care center in saurastra region. An informed parental consent was obtained from every case before the study. Ethical approval was taken from ethics committee of the institute.

Inclusion criteria for the study were patients with known case of β-Thalassemia major, Age ranging from 2 to 40 years, Undergoing regular blood transfusion, Taking chelation therapy for the past 6 months and Clinical follow up for at least 12 months before study.

Exclusion criteria for study were patients with Thalassemia Intermedia, not under regular blood transfusions and not taking chelation therapy for last 6 months.

All subjects underwent the following

- **Complete history taking:** A questionnaire was planned to fulfil.

1. Demographic data: name, age, sex, consanguinity and positive family history of thalassemia.
2. Medical history: age of onset duration, age of start of blood transfusion, and its frequency, history of splenectomy and history of liver affection.
3. Regimen of management: type of therapy received, including chelation therapy (dose, age of start, complications and compliance).

- **Complete physical and clinical examination:** Thorough clinical examination with particular emphasis on presence of pallor, jaundice, and signs of thalassemic features. Abdominal examination for hepatosplenomegaly.
- **Laboratory investigations:** Blood was collected by venipuncture in plain vacuette and EDTA vacuette. The serum was separated from the plain vacuette; hemolysis of the RBC was avoided. Care was taken to ensure that the serum samples are not contaminated. Collection tubes were iron free. Serum stored in Stopper tubes at 2-8 °C till time laboratory investigations which included:

1. Iron status as indicated by serum ferritin level which was evaluated three monthly over the period of the study.
2. Detection of hepatitis viral infection by Hepatitis B surface antigen (HBsAg) and RNA-PCR testing for HCV positive and HIV patients, which was done initially at the beginning of the study.
3. Complete blood count was done at the beginning and end of the longitudinal study (from the EDTA Vacuette) to evaluate for the changes in haematological parameters namely Hemoglobin (Hb), Packed Cell Volume (PCV), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH) and Mean Corpuscular Hemoblobin Concentration (MCHC). Complete blood counts were evaluated from Horiba 5 part Penta XLR analyser.

Serum ferritin level

1. Diametra, CA06034, Italy, Direct immune enzymatic determination of ferritin in human serum or plasma.
2. Hepatitis B surface antigen (HBsAg): Prechek Bio, Inc. CA92806, USA, Diagnostic kit for hepatitis B virus surface antigen (ELISA), one-step incubation, double-antibody Sandwich principle.
3. HCV-PCR: Qualitative estimation of HCV-RNA in serum was detected by nested RT-PCR assay.
4. HIV-PCR: Qualitative estimation of HIV in serum was detected by nested RT-PCR assay.

Statistical analysis

Data were analysed using the statistical package for social science (SPSS). Computer software package SPSS 15.0 was used in the analysis. For quantitative variables, mean, standard deviation, minimum, and maximum (as measures of variability) were presented. Frequency and percentages were presented for qualitative variable. ANOVA, Independent T, Mann-Whitney and Kruskal Wallis tests were used to estimate differences in quantitative variables. Chi-square and test was used to estimate differences in qualitative variables. Spearman's rank correlation test was used to determine the relationship between different numerical variables. For all tests, probability values (P) of less than 0.05 were regarded as statistically significant.

Observation and Results

In present study out of 90 patients, 54 patients were males and 36 patients were females. Mean age of 15.26 ± 7.04 years with ages range of 2-36 years and 8 and 12 years of age having the maximum incidence.

Transfusion frequency

It refers to the number of transfusion required by a patient in course of 1 month. It was observed in the current study that 68.9% (N = 62) of cases required twice monthly transfusion, 30.0% (N = 27) cases required once a month transfusion while only 1 case had thrice a month transfusion 1.1% (N = 1). It was observed in that a higher frequency of transfusion (twice per month) was seen in the older ager group and lower frequency (once per month was seen) in the younger patients.

Chelation therapy

It was also observed that the younger age group patients required lesser dosage of chelating agent at a lower transfusion frequency (once per month) compared to older age group patients who require higher dose of chelating agents.

Blood group

Out of the 90 cases, 16 had A+(17.8%), 10 had AB+ (11.1%), 26 had B+ (28.9%) and 36 had O+ (40%) blood group respectively. 25 cases were found to be HCV+ (27.78%), 3 were HIV+ (3.3%) and 62 cases were n on-reactive (68.89%). Maximum incidence of HCV reactive cases were seen in 5-14 years (14 cases) age group followed by 20 – 24 year age group with 5 cases [Table-1].

Table 1: Blood group with sero status

		Blood Group						Total
		A-	A+	AB+	B-	B+	O+	
Sero status	NR	1	9	8	1	18	25	62
	HCV + ve	0	7	2	0	8	8	25
	HIV + ve	0	0	0	0	0	3	3
Total		1	16	10	1	26	36	90

Age at the time of diagnosis

It refers to time at which the patient was labelled/diagnosed as case of thalassemia. Most frequently the cases were diagnosed by 3 months of age or at 6 months of age. 54 cases were diagnosed with β-thalassemia major by the age of 1 year. However exceptionally 1 case was diagnosed at 9 years of age as thalassemia major.

Splenectomy

15 cases (16.67%) were known to undergone splenectomy 74 cases (82.2%) were having variable degrees of Splenomegaly. However, 1 case (1.1%) was found to have splenic varices on ultrasonography.

CBC Parameters

In the present study in multi transfused diagnosed patients of beta thalassemia major, random consecutive 2 times pre transfusion CBCs were taken to compare and to know the adequacy of transfusion.

First Pre-Transfusion CBC

The distribution of RBC (*10^6 cells/µL) is normal with mean 3.52 and standard deviation 0.70045. The distribution of Hb (gm %) is normal with mean 9.14 and standard deviation 1.8368. The distribution of HCT% is normal with mean 28.076 and standard deviation 5.4033. The distribution of MCV (FL) is normal with mean 79.501 and standard deviation 5.5188.The distribution of MCH (pg) is normal with mean 26.783 and standard deviation 6.1443. The distribution of MCHC is normal with mean 32.892 and standard deviation 1.8609 [Table -2].

Second Pre-Transfusion CBC

The distribution of RBC (*10^6 cells/µL) is normal with mean 3.578 and standard deviation 0.68. The distribution of Hb (gm %) is normal with mean 9.09 and standard deviation 1.84. The distribution of HCT% is normal with mean 27.65 and standard deviation 5.37. The distribution of MCV (FL) is normal with mean 77.73 and standard deviation 8.708. The distribution of MCH (pg) is normal with mean 25.78 and standard deviation 2.098. The distribution of MCHC is normal with mean 32.98 and standard deviation 1.706 [Table-2].

It was observed that values like Hb, HCT% and RBC Count were dependent on factors like sampling time and point of sampling (i.e. before or after the transfusion) hence these tend to show no effect with the number of transfusions, average serum ferritin level throughout the year, age or sex and dose of chelating agent. MCV and MCH were found to be low normal values (in case of MCV) and moderately reduce (MCH), and were not found to be dependent on transfusion frequency, chelation therapy or ferritin values. MCHC values were found fairly constant with not much variation in values irrespective of point of sampling, transfusion frequency, serum ferritin values and chelating agent used.

Table 2: Various RBC parameters with minimum and maximum value along with mean and standard deviation

Descriptive Statistics						
Parameters	Number	Minimum	Maximum	Mean		Std. Deviation
	Statistic	Statistic	Statistic	Statistic	Std. Error	Statistic
RBC (*10^6 cells/µL)	90	2.11	5.49	3.5220	0.07383	0.70045
Hb (gm %)	90	3.5	13.2	9.140	0.1938	1.8386
HCT%	90	17.9	40.0	28.076	0.5696	5.4033
MCV (fl)	90	59.5	92.2	79.501	0.5817	5.5188
MCH (pg)	90	19.2	81.0	26.783	0.6477	6.1443
MCHC (g/dL)	90	23.3	37.1	32.892	0.1962	1.8609
Dose (chelating agent)	90	250	2000	1040.28	50.196	476.199
Serum ferritin levels	90	266.0	20318.0	4716.014	337.1783	3198.75
Yearly Average Serum Ferritin	90	361.75	14523.68	4724.84	287.65	2728.97

Assessment of adequacy of transfusion

On first pre and post transfusion CBC: On using the cut off of 10 gm % Hb as a marker to classify patients for adequate chelation therapy, we found that 30 cases (33.33%) were found to be adequately transfused with levels > 10 gm%. Of these 12 cases were females and 18 cases were males. There was no particular age distribution of adequacy of transfusion however maximal adequacy was seen in the age group of 12-20 years.

On second pre and post transfusion CBC: On using the cut off of 10 gm % Hb as a marker to classify patients for adequate chelation therapy, we found that 34 cases (37.78%) were found to be adequately transfused with levels > 10 gm %. Of these 13 cases were females and 21 were males. There was no particular age distribution of adequacy of transfusion however maximal adequacy was seen in the age group of 23-30 years.

Serum ferritin levels and chelation therapy effects

Final Ferritin (4th) evaluation which was done had an average value of 4716.01 ± 337.17 ng/mL. Mean of average yearly average ferritin values in the study duration was found to be 4724 ± 287.65 ng/mL. Serum Ferritin levels were found to be significantly correlated with transfusion frequency with p values = 0.002. Higher Serum ferritin levels were generally found in patients with 2 or more transfusions per month. Serum Ferritin values were found to be significantly correlated with drug and dose of chelating

agent p values < 0.001.
The trend of Serial Serum Ferritin monitoring was monitored in these 90 patients for over a year and it was found that while 40 patients show an increasing trend of Serum Ferritin levels 50 patients had a decreasing trend owing to their adequate chelated status.

Chelation therapy
Out of 90 cases all the cases were on some form of chelation therapy. All of the patients were on oral Deferasirox tablets (89), titrated against their serum ferritin levels, provided from our medical college. However, 3 cases were on same drug by trade name Asundra (showing excellent response) and 1 case showed inadvertent drug allergy to Asundra. Only 1 patient was on Kelfer (Deferiprone). The distribution of Drug Dose is normal with mean 1040 mg and standard deviation 476.19. The chelation therapy was independent of the number of transfusions given to different patients. The dose of cheating agent was directly found to be related to Serum ferritin levels.

Serum ferritin levels
The serum ferritin was assayed 3 monthly over a period of 1 year by ELISA method. It was found that Serum Ferritin levels could be correlated linearly with the chelation therapy and the dose of cheating agent. Higher the ferritin levels more chelating agent was required by the subject**.** Serum ferritin showed no relation to the number of transfusions to a patient who had well balance/ titrated doses. We used Serum Ferritin to grade the patients in 3 groups of patients as described in table-3.

Table 3: Serum ferritin levels in various groups of patients

Serum Ferritin (Range)	Number of cases	Monitoring Chelation therapy Interpretation
< 1000 ng/mL	03	Monitor Ferritin monthly, titrate to a lower dose
1000-2500 ng/mL	12	Monitor ferritin 3 monthly
> 2500 ng/mL	75	Monitor Ferritin 2-3 monthly check with LIC 6 monthly and Intensive chelation.

Discussion
Thalassemia are common genetic disorders in the World and Indian subcontinent. The distribution of β-thalassaemia gene is not uniform in the Indian subcontinent. The highest frequency of β-thalassaemia trait is reported in Gujarat, followed by Sindh, Punjab, Tamil Nadu, South India and Maharashtra. In various parts of India, the prevalence of β-thalassemia is different: 6.5% in Punjab, 8.4% in Tamil Nādu, 4.3% in South India, and 3.5% in Bengal. β-Thalassaemia has a high prevalence in some communities, such as Sindhi, Lohana, Tribes, and Rajputs [9].
Over the last 20 years, management of thalassemia major has improved to the point where patients' life expectancy will reach that of the normal population. These outcomes result from safer blood transfusions, the availability of three iron chelators, new imaging techniques that allow specific organ assessment of the degree of iron over load [10].
There is severe degree of anaemia, which is typically hypochromic and microcytic with a low mean cell haemoglobin (MCH) and mean cell volume (MCV). The red-cell indices derived from electronic cell counters may not always reflect the degree of haemoglobinization of the red cells. Many factors may be involved in this discrepancy, particularly heterogeneity of cell populations, with large numbers of extremely small cells which can not be seen by the electronic cell counter and also artefacts produced by the large numbers of nucleated red cells, white cells and platelets which are nearly always present after splenectomy [8].
The main aim for monitoring blood parameters in thalassemia major patients is to adjust and maintain the adequacy of transfusion. The optimal transfusion regimen for thalassemia major is still matter of discussion. Now a days undertrasfusion or moderate transfusion regimens with baseline Hemoglobin in the range of 8 to 10 g/dL [11]. In the present study the two random timely pretransfusion samples data suggests mean hemoglobin were ranged between 9 to 10 g/dL along with slightly lower side of MCV and MCH while MCHC being the most constant parameter.
In the treatment of thalassemia major, major concern is iron overload which should constantly monitored and maintained within limits by phlebotomy or chelation therapy. Depending upon the organ, it can take a long time to significantly reduce iron, so the best strategy is acting early and, in fact, trying to prevent significant iron loading from the start [12]. Effective management of iron overload requires frequent evaluation of the body iron stores [13]. There are few quantitative, non-invasive methods for measuring body iron that are safe, accurate and readily available for example Serum Ferritin.
In any event, when serum ferritin is greatly increased, whatever the reason, there is cause for concern and an increasingly aggressive iron chelation treatment should be given. In a study by Bandyopadhyay *et al.*, patients even in the younger age group showed high serum ferritin levels. They found that in 1-5 years age group, average serum ferritin was 1750 ng/ml, and this increased to 3650 ng/ml in 11-15 years older patients [14]. The serum ferritin level could not be controlled well as only few patients fully complied with recommended regimen at home [320]. The values in our study are comparable with similar regional and international studies. In our study the Average of the Serum ferritin (in the last assessment was 4716.01 ng/mL and the mean of the yearly average ferritin level of all the patients was 4724.84 ng/mL.
Also in this study all of the patients (100%) were taking some form of chelation therapy provided by the government setup at thalassemia ward. Approximately 3.33% (3 cases) of patients were under adequately chelated, 13.33% (12 cases) of cases were under controlled chelation and required follow up with serum ferritin levels and 83.33% (75 cases) were having very high levels of ferritin > 2500 ng/mL and required aggressive chelation therapy. Comparing this to the research by Shah N, *et al.* [15] at IRCS, Ahmedabad. In their our study 96 (67%) patients were taking some form of chelation therapy. Out of these 96 patients taking chelation, only 2 (2%) are taking adequate chelation and hence the dose and/or the type of the chelating agent(s) needs to be modified in 94 of the patients already on chelation therapy. Out of the remaining 46 (33%) patients, only 7 have maintained adequate ferritin levels (< 1000 ng/ml) without chelation.
It was found that only 2.2% cases (2 cases) were classifiable as adequately chelated and adequately transfused individual, 35.56% cases (32) were inadequately chelated and adequately transfused. A major percentage of the patient population 62.22% (56 cases) were inadequately transfused and inadequately chelated.

There are other problems associated with hyper-transfusion for example transmission of Transfusion transmitted infections (TTIs) like HCV, HIV and HBV also transfusion associated reactions are no infrequent. While infection transmission and mis-matched transfusion which can be avoided by good blood banking practices. In our study we found none of the patients to have developed transfusion related reactions or mismatched transfusion. Only 3% cases were on triple saline washed blood component and its incidence was seen in patients >24 years (total number of transfusions > 600) of age maybe owing to all immunization. We found the incidence of HCV to be 27.78%% (25 cases) and 3.33% HIV (3 case). This large number of thalassaemic patients having HCV in a post testing era is a worrisome as it has an additive effect in iron overloaded patients.

Table 4: Comparison of various studies of seropositivity of multiple transfused beta thalassemia major patients

	Study, Country	Year of Publication	Number of Patients Studied	HCV Sero-positivity Percentage
1	AH Mollah, *et al.*, Bangladesh [16]	2003	259	12.5
2	M Shayyab Al, *et al.*, Jordan [17]	2001	143	40.5
3	TN William, *et al.*, India [18]	1992	54	11.1
4	M Ansar, *et al.*, Iran [19]	2002	105	63.8
5	M Irshad, *et al.*, India [20]	2002	50	30
6	S Okada, *et al.*, Myanmar [21]	2002	-	55.5
7	Present study	2021	90	27.8

In India, mandatory screening for HCV was introduced as late as 2002. The prevalence of HCV was found to be as high as 21% in thalassemia patients and correlated with advancing age, indicative that they may have acquired it in the period when screening of blood units for HCV was not mandatory [22]. The high HCV incidence maybe due to the lacunae in testing for TTI. In our study maximum incidence of HCV reactive cases was seen in age group of 10-14 years followed by 15-19 and 20-24 years.

Limitations

There were a few limitations we met while in this study namely, the height and weight of the subjects could have been kept in record to accurately monitor the dose of the chelation therapy. The seropositivity status of the patients was not known as to when they have contracted it which could have been of importance to know the source and cause of this high seropositivity. To expand the dimension of the effects of blood transfusion and chelation therapy we could have use other parameters like SGPT, SGOT Serum Urea, Serum Uric acid, Radiological investigation like T2 Star MRI and if consented advise for liver biopsy for accurate titration of Iron loads. The patients here lacked the motivation to go for a bone marrow aspiration and liver biopsy. We could have taken a cohort of patients with different chelation therapies so as to study the efficacy different drugs have to control the increasing serum ferritin.

Conclusions

In the present study, it is concluded that Haematological parameters like Haematocrit, Red Blood Cell mass, Haemoglobin and Mean Corpuscular volume had large covariances while Mean Corpuscular Haemoglobin and Mean Corpuscular Haemoglobin Concentration show very narrow covariance. Serum Ferritin levels was positively correlated with chelation therapy and transfusion frequency among the thalassaemic patients as well as Serial Serum Ferritin Levels is to be used to set up a base line and monitor trend of iron reserves in patients with subsequent transfusions. There is a rapid increase and high prevalence of HCV Seropositivity among the thalassaemic patients despite the screening of blood for transfusion transmitted infections proper blood banking and strict anti HCV testing for donors and screening of samples must be done to prevent further transmission.

Conflict of Interest

Not available

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Not available

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