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Original research article

Transfusional Iron Overload- A Major Issue in Multi - Transfused Beta Thalassemia Patients

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Abstract

Introduction: In β-thalassaemia major, repeated blood transfusions, ineffective erythropoiesis and increased gastrointestinal iron absorption lead to iron overload in the body. In developing countries like India with limited availability there is still reliance on the serum ferritin level as a means of monitoring the iron overload and the efficacy of chelation.

Objective: The aim of the study was to measure the ferritin levels in multi-transfused β-thalassemia major as an indicator of transfusional iron overload. To study the association of serum ferritin level with various variable, complications due to repeated transfusion, compliance of patients to iron chelation therapy.

Materials And Methods: A total of 60 β-thalassemia Major patients registered at the tertiary care centre for blood transfusion who received more than 10 units of blood transfusion were included in this cross sectional study. Parameters studied were serum ferritin level, seroconversion for transfusion transmitted infections and complications such as deranged thyroid function test, liver function test and cardiac function.

Results: The mean serum ferritin levels were 3801+/- 1675.20. 77.35% (41/53) were compliant to the iron chelation therapy. The mean ferritin levels in compliant versus non compliant patient was 3773.87 ng/ml and 3695.05 ng/ml. The thyroid function test was abnormal in 9.43 % (5/53), Liver function test was deranged in 49.12% (28/57) and 2D Echo for heart function was abnormal in 14.28% (3/21) patient. 2 patients (3.33%) were sero-positive, one for HCV and second for HIV antibody.

Conclusion: There is a need for better quantitative indicators, non-invasive methods, accurate and which are readily available along with development of newer chelating agent for better compliance and efficacy. Antenatal diagnosis, increase awareness among patient and relative, adequate provision of medical care facility, adherence to standard treatment protocol and Bone Marrow Transplant may result in effective management of the thalassemia patient.

Keywords: β-thalassemia Major, Ferritin, Iron chelation therapy, Sero-positive

Introduction

Beta-thalassemia is still one of the major health problem in developing countries. Beta-thalassemia's (β-thalassemia's) are a group of inherited blood disorders caused by reduced or absent synthesis of the beta chains of hemoglobin resulting in variable phenotypes ranging from severe anemia to clinically asymptomatic individuals [1].

The homozygous form of deficient beta-chain synthesis, which is very severe and presents itself during childhood. Tissue iron overload inevitably occurs in patients who receive regular red cell transfusion. In β-thalassemia major, repeated blood transfusions, ineffective erythropoiesis and increased gastrointestinal iron absorption lead to iron overload in the body. Alternatives to blood transfusions include splenectomy, HSCT (Hematopoietic stem cell transplantation), and Hydroxyurea [2]. Although the survival of thalassemics is steadily increasing, the prevalence of complications due to iron over load remains high. Uncontrolled iron overload has serious clinical consequences resulting in significant morbidity and mortality. The management of the iron overload in these patients requires the administration of iron chelators continuously and evaluation of serum ferritin levels at regular intervals. In developing countries like India with limited availability of noninvasive measures of hepatic and cardiac iron, there is still reliance on the serum ferritin level as a means of monitoring the iron overload and the efficacy of chelation.

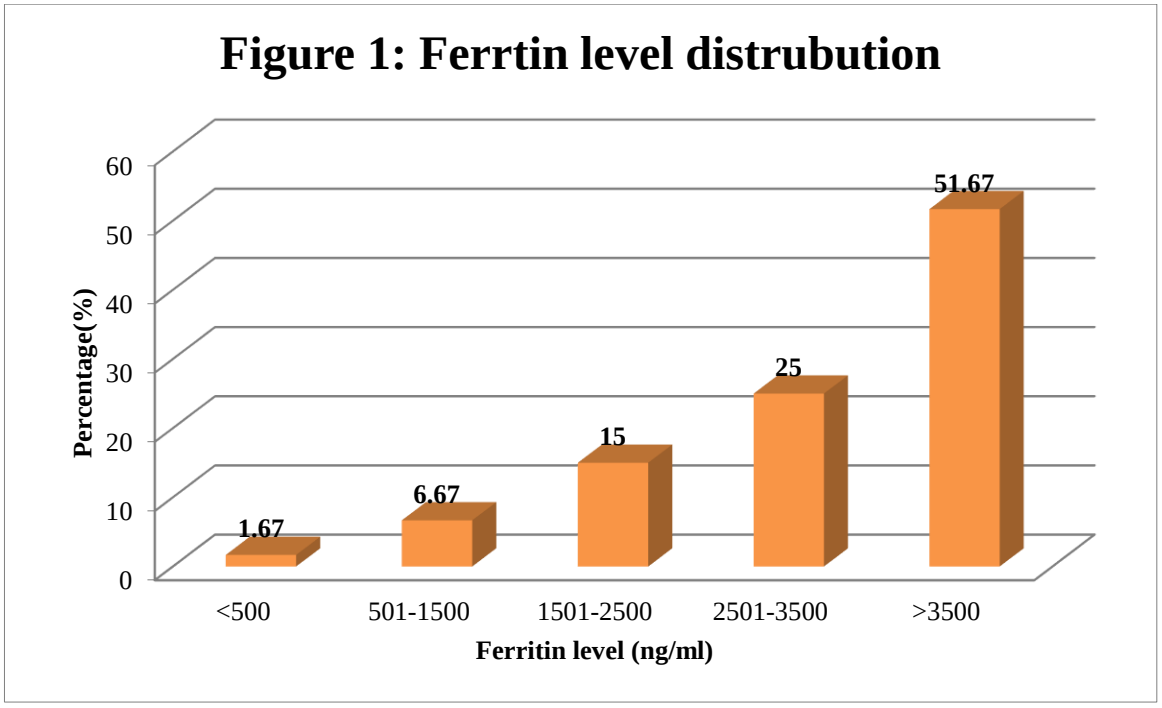
Material and Method

A total of 60 cases of known β-thalassemia major patient were included in this cross sectional study. The study was conducted at a tertiary care hospital in Mumbai, Western India. β-thalassemia patients registered at this Centre for blood transfusion who received more than 10 units of blood transfusion as part of their management were included in the study. 3 ml of patient's venous blood sample was collected by a clean venipuncture and serum ferritin levels were estimated by ELISA technique.

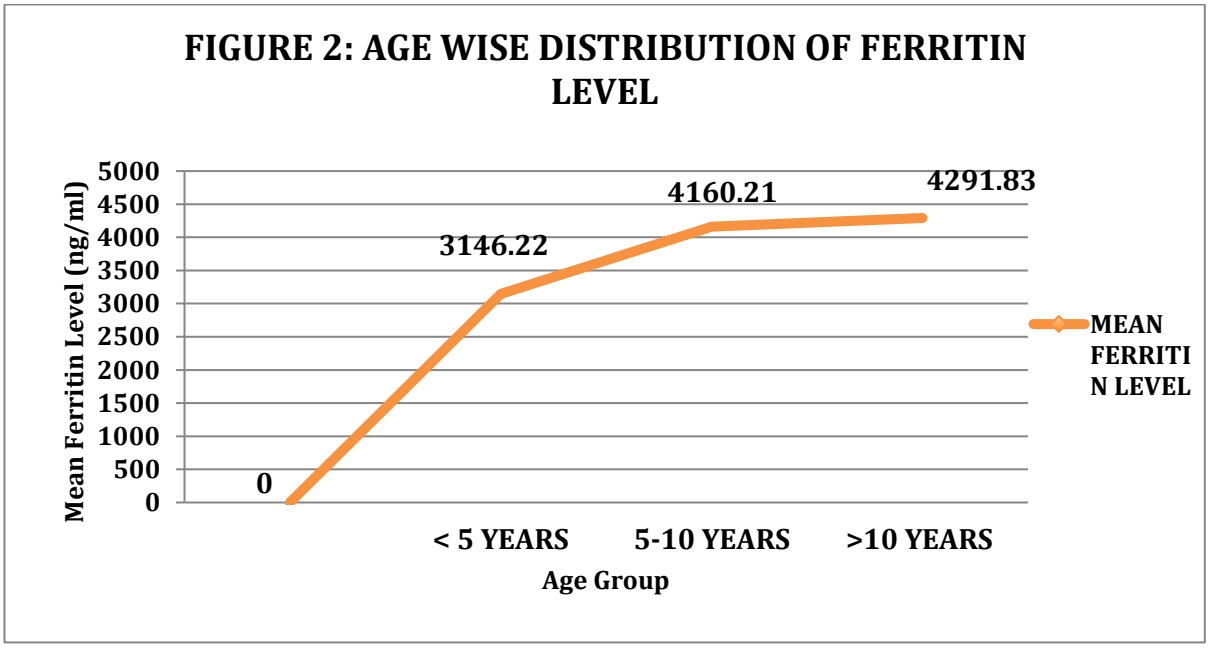
Parameters studied were Serum ferritin level, any seroconversion for transfusion transmitted infections (TTI) such as Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), and Hepatitis C Virus (HCV) infections and occurrence of complications such as deranged thyroid function test, liver function test and cardiac function. Data regarding clinical details of patients, complication, record of iron chelation therapy, thyroid function test, liver function test and cardiac function was collected from patients case record file. Patients who have not consented to participate were excluded from the study. The aim of the study was to measure the ferritin levels in multi-transfused β-thalassemia major as an indicator of transfusional iron overload. To study the association of serum ferritin level with various variable, complications due to repeated transfusion, compliance of patients to iron chelation therapy.

Result

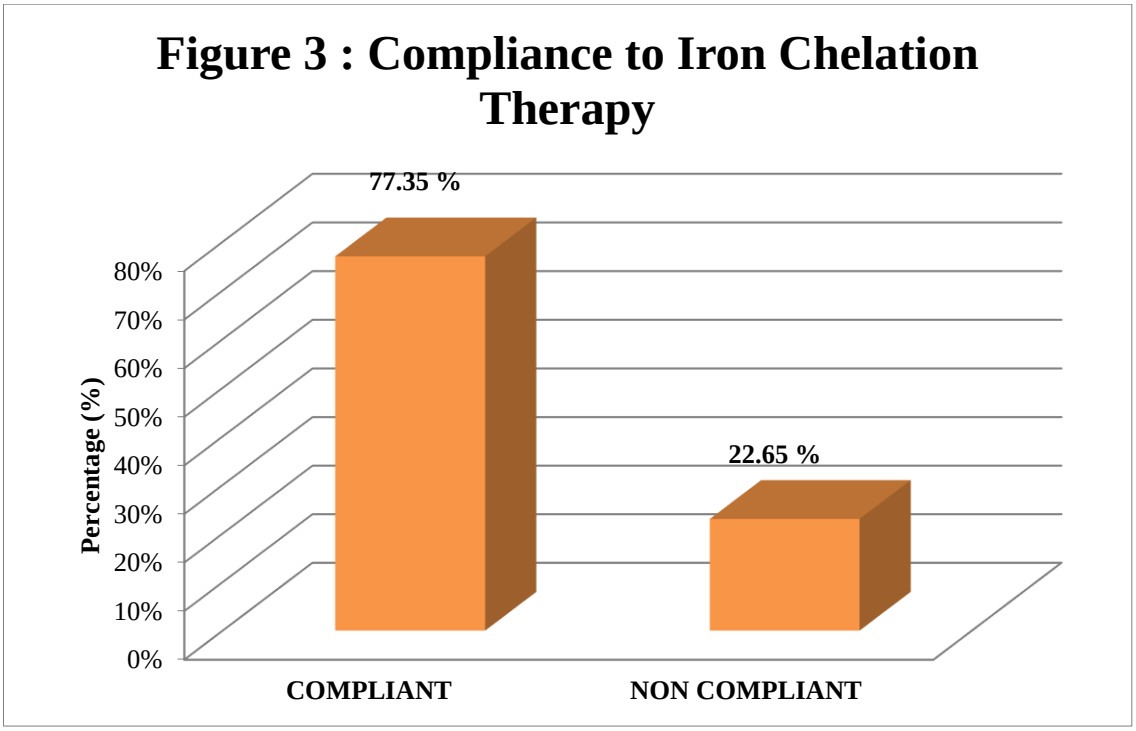
In a total of 60 cases studied, 32 were males and 28 females with a male to female ratio of 1.14: 1. The age of patients at the time of diagnosis ranged from 3 month to 3 years. The age at the time of this study ranged between 1 year 4 months to 16 years.10% (6/60) patients were not confined to the center; they received transfusion from other center also.



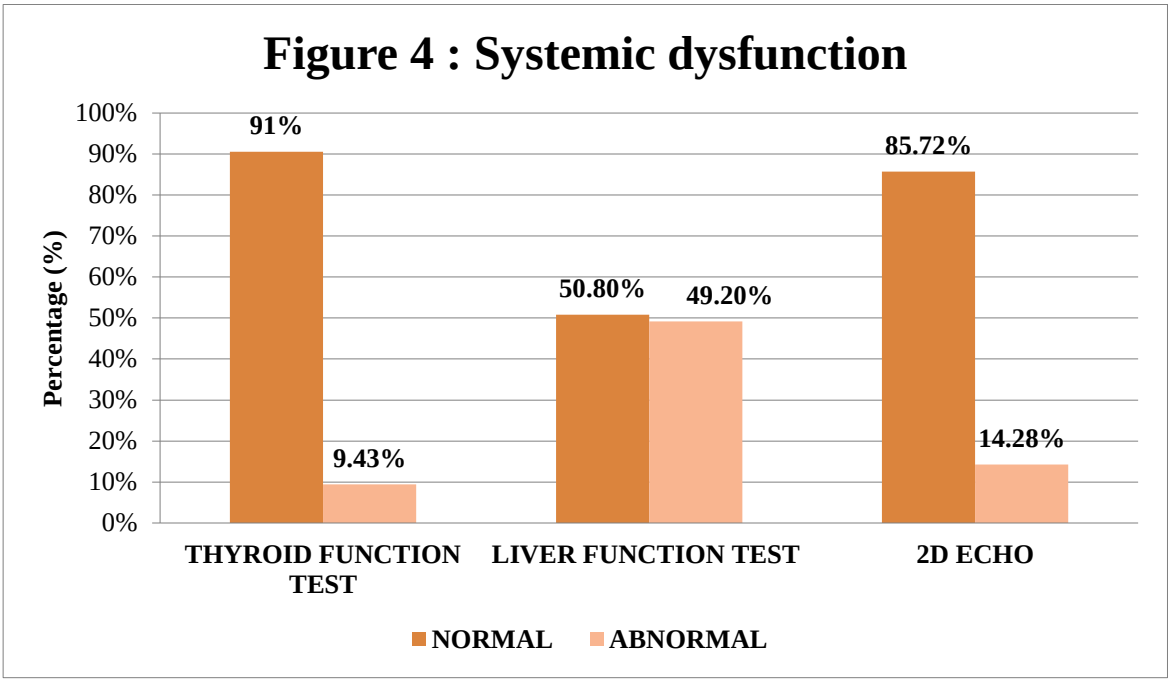
The mean serum ferritin levels were 3801 (SD +/- 1675.20) ng/ml . Only one patient (1.67%) had serum ferritin levels of less than 500 ng /dl, four patients (6.67%) had levels between 500-1500 ng/ml, nine patients (15%) had levels between 1501-2500 ng/ml, fifteen patients (25 %) had levels between 2500-3500 ng/ml, while remaining 31 patients (51.67%) had levels more than 3500 ng/ml. (Figure 1)



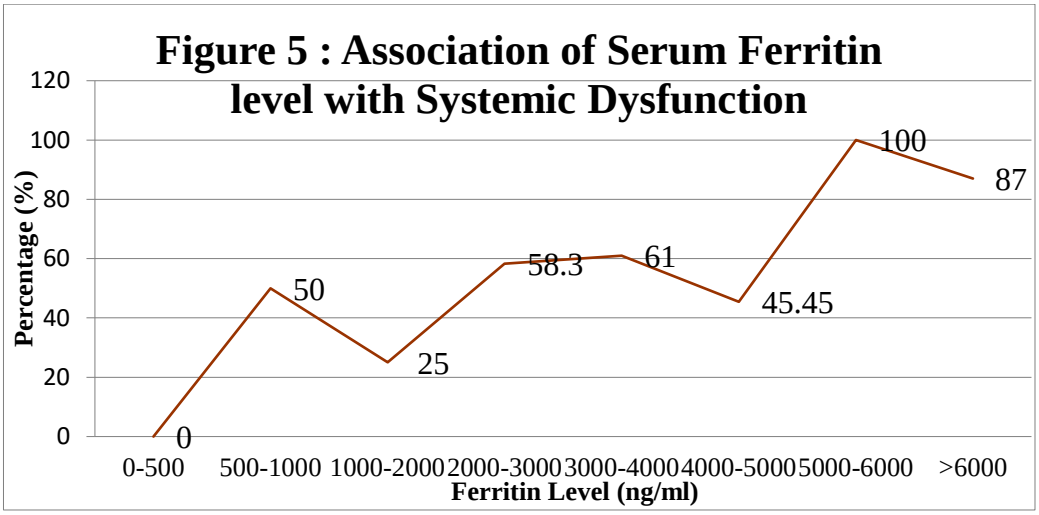
The mean ferritin level in age group below 5 years was 3146.22 ng/ml, in age group between 5 years to 10 years was 4160.21 ng/ml and in age group more than 10 years was 4291.83 ng/ml. The serum ferritin level increases as the age of the patient increases as depicted in Figure 2.



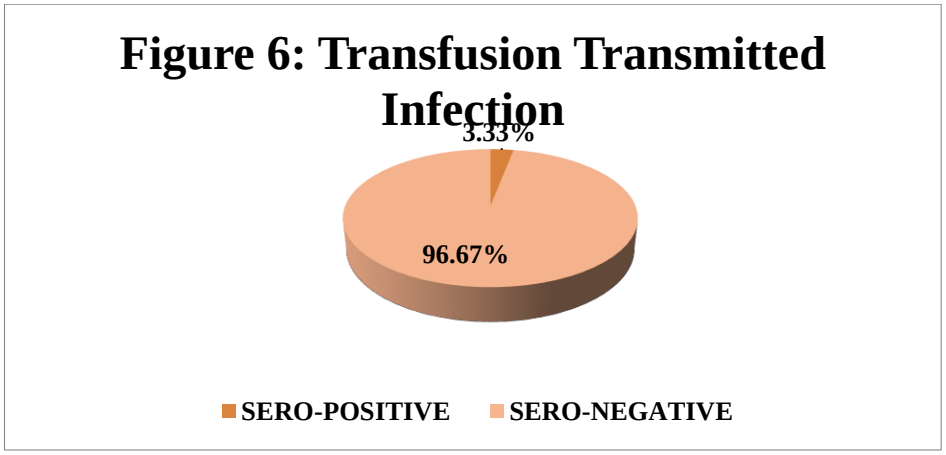
Most of the patient were complaint to the iron chelation therapy and used regularly. 77.35% (41/53) were compliant to the iron chelation therapy were as 22.65 % were non compliant to the therapy (Figure 3). The mean ferritin levels in compliant versus non-compliant patient was 3773.87 ng/ml and 3695.05 ng/ml and the co-relation between two variables was statistically insignificant (Unpaired t- test).



The thyroid function test was abnormal in 9.43 % (5/53). Liver function test (LFT) was deranged in 49.12% (28/57) patients. The 2D Echo for heart function was abnormal in 14.28% (3/21) patient (Figure 3).



None of the study population was having systemic dysfunction with ferritin level below 500 ng/dl, 50% were having systemic dysfunction with ferritin level between 500-1000 ng/dl, 25% with ferritin level between 1000-2000, 58.3% with ferritin level between 2000-3000, 61% with ferritin level between 3000-4000, 45.45 % with ferritin level between 4000-5000, 100% with ferritin level between 5000-6000 and 87% with ferritin level above 6000 ng/dl. Overall prevalence of systemic dysfunction was higher with high serum ferritin levels. (Figure 5)



2 patients (3.33%) were sero-positive, one for HCV and second for HIV antibody. The cause for sero-positivity was mainly transfusion related. (Figure 6)

Discussion

The goals of transfusion include correction of anemia, suppression of erythropoiesis and inhibition of increased gastrointestinal absorption of iron. For patients of beta thalassemia major different transfusion protocols are suggested. "Hypertransfusion" and "Supertransfusion" regimens achieve the goals of anaemia correction and suppression of erythropoiesis but are associated with substantial iron loading. In a study by Amit Kumar et al., the mean serum ferritin level was 2767.52 (SD 1849.1) ng/ml [3]. In our study, the mean serum ferritin level was 3801+/- 1675.20 ng/ml, which is markedly higher than the normal recommended levels for normal individuals. Normal values of serum ferritin for men and women are 12-300 ng/mL and 12-150 ng/mL, respectively [4]. Patients with β-thalassemia on a typical blood transfusion schedule accumulate iron at a rate of 0.3–0.6 mg/kg of bodyweight

per day [5,6]. Excess iron within the body is toxic at levels above 12–24 g of total body iron [5,6].

In many places, the patient's reports to blood centers for blood transfusion in a haphazard manner. Prognosis varies; however, the younger the child at disease onset, the less favorable the outcome. In the absence of or due to inadequate iron chelation therapy the accumulation of iron results in progressive dysfunction of the heart, liver and endocrine glands. As the mean ferritin levels in compliant patient was 3773.87 ng/ml and non-compliant was 3695.05 ng/ml in our study, which was statistically insignificant. Reason might be due difference in the dosage of iron chelation therapy, frequency of blood transfusion or discontituation of treatment because of concern over effectiveness of treatment or low iron levels. To optimize the Iron Chelation therapy it is recommended that patient receiving more frequent transfusions must receive dose adjustments of iron chelators based on serum ferritin trends and assessment of safety markers.

Iron overload can also result in arthropathy, neurodegenerative disorders, hyperpigmentation, pulmonary hypertension and carcinogenesis [7,8]. Iron accumulates in tissues with high levels of transferrin receptors such as the liver, heart, and endocrine glands. Decreased expression of hepcidin, a key regulator of iron homeostasis, promotes intestine iron absorption, even in the presence of iron overload [9]. Some preclinical trials have shown that hepcidin mimetic and TMPRSS6 (Transmembrane Serine Protease Matriptase-2) inhibitors can reduce ineffective erythropoiesis, anemia, and iron overload. Moreover, synthetic hepcidin is still in phase 2 clinical developments. Iron induces inflammation with significantly increased levels of proinflammatory cytokines (IL-1, TNF-alpha, and IL-6), which might result in the gradual and progressive deterioration of organ function in Thalassemia Major [10,11]. Many studies concluded that cirrhosis of liver is associated with increase in serum ferritin levels [12]. In our study we found one patient sero-reactive for HIV antibody and one patient for HCV antibody. Incidence in a study by Bandyopadhyay et al was 1.75% in the age group of 1 to 5 years and 2.08% in the age group of 6 to 10 years for Hepatitis C virus [13]. Seroprevalences of HIV, HBsAg, HCV and Syphilis in different studies are shown in the Table 1.

Table 1: Seroprevalences of HIV, HBsAg, HCV and Syphilis from various studies

	Country	HIV	HBsAg	HCV
Borgna-Pignatti et al [14]	Italy	1.7 (12/720)	-	44.6 (100/224)
Bejaoui and Guirat [15]	Tunisia	0 (0/391)	2.3 (9/391)	6.1 (24/391)
Shah et al [16]	India	2 (3/142)	2 (3/142)	45 (64/142
Zou et al [17]	USA	2.16 (Incidence per 100,000 person years)	2.62 (Incidence per 100,000 person years)	2.98 (Incidence per 100,000 person years)
SHOT [18]	UK	0.18/1,000,000 donations	0.79/1,000,000 donations	0.025/1,000,000 donations
Ahmed Kiani et al [19]	Pakistan	0.5 (6/1253)	3 (38/1253)	21.7 (273/1253)
Politis [20]	Greece	0.3 (NR/1321)	1.8 (NR/1321)	54 (NR/1321)
Present Study	India	1.6 (1/60)	0 (0/60)	1.6 (1/60)

NR, not reported.

Multiple transfusions in thalassemia major patients are at a risk of developing TTI including HIV, HBV, and HCV [21]. Donor risk assessment and strict criteria of safe donor selection have to be adopted in order to minimize risk of TTI [22]. Infection in donated blood may not be detected due to the collection of the donation during the window period of infection or failure due to assay sensitivity or error. The reason for increasing incidence might be due to increasing number of transfusion. Some transfusion medicine experts have proposed that certain populations, particularly sickle cell and beta- thalassemia patients, receive units that are phenotypically matched. These patients, who are transfused repeatedly, seem more likely to make alloantibodies than the general population. Effective management of iron overload requires frequent evaluation of the body iron stores. Serum ferritin measurement, although easy to perform frequently, has too great a variability, but at present, no other serum/plasma marker is a better predictor of the total body iron [23]. The serum ferritin level could not be controlled unless the patients are fully complied with Iron Chelation Therapy regimen. It appears in our study that perhaps chelation therapy is the most deficient area of conservative thalassemia management. Newer oral preparation iron chelating agent might help to change this scenario.

Conclusion

Assessment of iron overload is an important aspect of patient management. The iron status of the body in overload conditions can be assessed by different methods. Better indicator of iron overload than serum ferritin should also be considered in centers having facilities such as LIC (Liver iron concentration), Heart function (Left Ventricular Ejection Fraction), cardiac MRI T2, NTBI (Non Transferrin Bound Iron). The liver is the major site of iron overload, containing 70% or more of body iron content. Liver iron correlates closely with total body iron in transfusional iron overload and total body iron. There is, therefore, a need for quantitative, non-invasive methods for measuring body iron that are safe, accurate, readily available along with development of newer chelating agent for better compliance and efficacy. The study also emphasizes on the importance of NAT in testing of blood especially to reduce the TTI in multi-transfused patients. Antenatal diagnosis, increase awareness among patient and relative, adequate provision of medical care facility, adherence to standard treatment protocol and Bone Marrow Transplant may result in effective management of the thalassemia patient.

Conflict of Interests

The authors declare that they have no competing interests.

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