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**Original Article**

# Effectiveness of Iron Chelation Therapy Using Serum Ferritin Levels in Thalassemia Major Patients

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**Abstract:**
**Objective:** Is to evaluate the effectiveness of iron chelation therapy in thalassemia patients using serum ferritin level at children hospital, Shaheed Zulfiquar Ali Bhutto Medical University, Pakistan Institute of Medical Sciences Islamabad
**Background:** -Thalassemia major is caused by defect in the synthesis of 1 or more the goblin subunits of hemoglobin, resulting in valuable phenol types lifelong RBC transfusion remain the main treatment for BETA thalassemia major patients' transfusion dependent patients in the absence of chelation therapy, develop progressive accumulation of iron, which is responsible for tissue damage. Prevalence of iron Induce organ damage ultimately resulting in iron toxicity. This iron toxicity produces myocardial siderosis and heart failure, liver cirrhosis and liver fibrosis and liver cancer osteoporosis and endocrine dysfunction and thromboembolism.
**Materials & Methods:** -The study was carried out at thalassemia center, children hospital, Pakistan Institute of Medical Sciences Islamabad January 2015-April 2016. All the patients that are enrolled in the thalassemia center were examined the Inclusion criteria of my study is those patients that are receiving iron chelation therapy. The exclusion criteria of my study are patients that are not undergoing iron chelation therapy.
**Results:**-Out of total 105 patients, 70 (67%) were receiving iron chelation therapy. in these 65(62%) and 40(38%) were males and females respectively. Majority of the patients showed very high ferritin level. The mean serum ferritin level was found to be **3650.14 ng/ml**. 65% of the patients have mean serum ferritin level less than 3000ng/ml, 27% of the patients have serum ferritin level between 3000-6000ng/ml, while 8% have ferritin level above 6000ng/ml. The observed highest average ferritin level is 7651ng/ml, while lowest is 1866ng/dl.
**Conclusion:**-A high percentage of the patients are receiving iron chelation therapy in PIMS but iron chelation therapy is not very effective. The study showed high levels of serum ferritin .There is a dire need to rationalize the iron chelation therapy.
**Key Words:** -Thalassemia, transfusion, iron chelation therapy, ferritin level

## Introduction

Thalassemia is a major health problem in world especially in developed countries. According to estimate 4.5% of world population is carrier of hemoglobinopathies. Huge numbers of thalassemia patient are seen in South Asia, especially in Pakistan. Thalassemia isan autosomal recessive heterogeneous group of hereditary disorder of decreased hemoglobin synthesis In South Asia there are 40 million carrier of thalassemia gene, due to the mutation in beta gene. Over 200 different genetic defects have now been detected which are caused by mutations in chromosome 11.

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Due to the mutation in beta gene, synthesis of beta goblin chain is suppressed and hence production of HbA is suppressed where as HbF and HbA2 is markedly increase.[1,19] This severe imbalance of globulin chain synthesis results in ineffective erythopoises, hemolysis and anemia. Transfusion therapy which is the treatment allows for the normal growth and development and suppresses ineffective erythopoises but leads to the iron excess in the body .[2]Red blood cell transfusions decrease the complications of anemia and compensatory bone marrow expansion, permit normal development throughout the childhood and extend the survival[3]. Under normal conditions there is no regulatory and rapid iron excretion in humans and body iron levels are mainly regulated from the absorption of iron from

the gut. In parallel transfusions result in a second disease while treating the first, that of the accumulation of tissue iron.[4]This without treatment is fatal, as it causes oxidative injury, tissue siderosis, hepatic cancer, endocrinological siderosis, diabetes, hypothyroidism osteoporosis, thromboembolism, spleenomegaly and cardiac failure.[5] In the 1960 century, Iron chelation therapy, was first introduced, initially, in short term studies in iron loaded patients. It increases urinary iron excretion, decrease serum ferritin level and reduces liver iron in majority of chronically transfused iron loaded patients. It extends the survival free of iron induce complications and dramatically improves quality of life, which are observed in well chelated patients.[6]

The assessment of iron overload is done by serum ferritin levels which have a direct co relation with the body iron stores. The serum ferritin level of 1000 ng/ml is taken as the cut off to indicate iron chelation therapy. Defroxine isa good subcutaneous iron chelator used for chelation therapy oral agents like deferipione and deferisirox is also available.

The rationale of my study is to evaluate the effectiveness of iron chelation therapy using serum ferritin levels done at thalassemia center children hospital, SZABMU, PIMS and to minimize the complications of iron overload, which could be a barrier for a definitive cure from thalassemia. Regular blood transfusion and iron chelation therapy appears to improve the survival in thalassemia major patients.

## Material & Methods

**Study Design:** This is a descriptive study involves retrospective analysis of 105 thalassemia patients who underwent repeated transfusions and iron chelation therapy after regular interval.

**Duration:** The study is conducted from January 2015 to April 2016.

**Setting:** The study is carried out at thalassemia center, children Hospital, Shaheed Zulfiquar Ali Bhutto Medical University (SZABMU), Pakistan Institute of Medical Sciences Islamabad. All patients were selected through convenience and non-probability sampling.

**Inclusion Criteria:** The inclusion criteria of my studies involve allthalassemia patients that were registered at thalassemia center, children hospital, PIMS from January 2015 to April 2016. All patients have been receiving multiple transfusions (at least 10) and are frequently taking iron chelation therapy.

**Exclusion Criteria:** The exclusion criteria of my studies involve those thalassemiapatientsthat were registered at thalassemia center, children hospital, PIMS from January 2015 to April 2016, who have receivedonly a few transfusions and do not need chelation therapy.

**Clinical Accounts:** The diagnosis of thalassemia was mainly based on Hb electrophoresis, history of family members and clinical examination. clinical details of the patients were recorded taking into account age, sex, residence, social status, family history, Hb, ferritin level , peripheral film, blood transfusion history, duration of disease and examination of spleen, liver, heart, chest, urea and creatine level, chelation therapy. Dosage of chelation therapy is adjusted according to the serum ferritin level, weight, and height of the patients. Detailed report of each thalassemia patient was analyzed and deeply studied. Complete data of each patient was first collected in a work sheet and then on a Performa so that record of a patient can be summarized. Afterwards a table was made containing the column of transfusion history, highest ferritin level, and average ferritin level of each patient in order to extract result. Finally mean serum ferritin level was calculated. The data was entered into SPSS version 20.

## Results

A total of 105patients were evaluated in the study duration, of these 70 (67%) were receiving iron chelation therapy while 35 (33.33%) were on blood transfusions only. Their age ranged from 5 months to 24 years. The most frequent age group was from 2-10 years in this study 65 (62%) were males while females constitute the 40 (38%) patients. Male to female ratio was 1.61:1 (62:38). The interval between successive transfusions varied from 30 -45 days commonly in different patients. All these 70 patients were receiving iron chelation therapy and dosage is adjusted according to the serum ferritin level of the patient and ferritin level is examined after every 3 months. Duration of transfusion, range of ferritin level and average ferritin level of each patient is mentioned in (Table 1).

**Table-1: History of Transfusion and Average Ferritin Levels**

| History of transfusion | Range of ferritin levels ng/ml | Average ferritin level ng/ml |
|---|---|---|
| Below 3 Years | 510-3518 | 1866 |
| 3-6 Years | 975-6644 | 3325 |
| 6-9 Years | 1074-7000 | 3480 |
| 9-12 Years | 1030-7197 | 2753 |
| 12-15 Years | 1010-6646 | 3234 |
| 15-18 Years | 1200-4100 | 3023 |
| 18-21 Years | 7241-8501 | 7871 |

The injection technique was incorrect in 28%, partially correct in 54% and correct in 18% of patients before education session.
After the education session injection technique was correct in 92% of patients. It was partially correct in 8% while no patient had incorrect technique. These results were statistically significant ($p<0.001$) when compared with one sample t-test (Table-2).

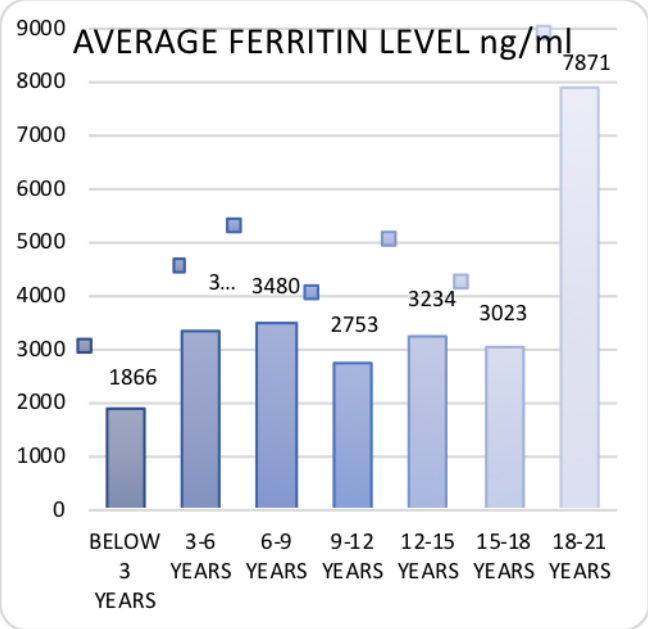


**Figure-1: Average Ferritin Levels According to the Transfusion**

The lowest ferritin levels were observed in patients on chronic transfusion below 3 years, while highest ferritin level was 7871 ng/ml in patients receiving transfusions from 18-21 years. Majority of the patients revealed very high ferritin levels with a mean of 3650.28ng/ml. 45(64.29%) patients have ferritin level less than 3000ng/ml, 20(28.57%) patients have ferritin level between 3000ng/ml, while 5(7.14%) patients have values more than 6000ng/ml(Table 2).

**Table-2: Serum Ferritin Level in Thalassemia Major Patients.**

| Serum Ferritin Levels ng/ml | Number Of Patients |
|---|---|
| <3000 | 45(64%) |
| 3000-6000 | 20(27%) |
| >6000 | 5(8%) |

These levels reflect inadequate iron chelation therapy and vulnerability to develop iron overload related complications.

# Discussion

Thalassemia present an increasing health problem in the tropical countries in which they occur at a high frequency. It is one of the commonest heterogeneous group of genetic disorder that result from a reduced rate of synthesis of beta goblin chains thus causing reduction in HbA which in turns lead in microcytic anemia. Microcytic anemia ultimately develops in respect to inadequate HbB synthesis.[7, 8]
The transfusions of packed red blood cells are the corner stone of thalassemia. Transfusion is necessary for the survival of the patients and to maintain an Hb level of 9 to 10g/dl. Annual transfusion of 10 to 20 units of packed red blood cells in children younger than 10yrs of age, and 25 to 50 units of packed red blood cells in teenagers and adults are generally administered. [9, 21]
The most important consequence of chronic transfusions in thalassemia patients is the inexorable, accumulation of iron. As humans have no mechanism other than slogging of the mucosa of their GIT track or menstruation to excrete excess iron. Patients who are being transfused every three or four weeks gains 0.5mg/kg per day of iron in excess of natural losses. This iron is very toxic to tissues, liver, heart, endocrine organs leading to a wide array of complications.[10, 20]
Detail analysis and complete record of the patients in the thalassemia center of Pakistan institute of medical sciences show every patient after 8 to 10 transfusions cannot maintains its plasma iron level within normal range. In our study the mean serum ferritin was **3650.14ng/ml** which is markedly higher than the normal recommended level of normal individual. Normal values of serum ferritin for men and women are 12-300ng/ml and 12-150ng/ml respectively.[11]Similarly markedly high ferritin level is reported in studies conducted locally and internationally. Nadeem Ikram, et al in 2003 at Islamabad and Rawalpindi reported the ferritin level to be 3390ng/ml.[12]Haris riaz, et al conducted a study in Karachi in 2011 the mean serum ferritin level was 4236.5ng/ml.[13]Amna faruqi, et al in Karachi in 2009 reported mean serum ferritin level to be 6062.61ng/ml[14].The ferritin levels observed in Rawalpindi and Islamabad are better than those observed in Karachi. In 2009, Lamis A Raqab, et al conducted a study in Egypt the serum ferritin level was 1728.66.[15]Ayindo KY et al in 2002 reported the mean serum ferritin level to be 1931ng/ml[16].Cunningham MJ et al, in 2004 observed mean serum ferritin level that was 1698ng/ml[17].These

international studies show better serum ferritin levels because they have better protocols and implementation due to better finance. In India Choudary VP et al in 2004 reported the mean serum ferritin level to be 6723 mg/ml, that is even higher than our studies in Pakistan.[18]

All the studies carried out in Pakistan and India as compared to other countries with better socio-economic conditions showed very high serum ferritin levels. A target ferritin level of approximate 1000ng/ml is generally recommended standard practice in thalassemia patients to initiate iron chelation therapy and keep them close to the target. [21]

**Limitations of the Study: -**

1. Patients compliance and duration since chelation started.
2. As ferritin is acute phase protein, patient's physical condition was not assessed at the time of testing.

## Conclusion

Iron chelation treatment is necessary to prevent iron overload and damage to the internal organ. With appropriate iron chelation, we can improve the quality of life of these patients. In our country the socioeconomic problem, low education level and inadequate provision of health care are the main hurdles in effective treatment of iron overload in thalassemia patients which are the main cause of morbidity and motility in thalassemia major. Iron Chelation therapy in thalassemia center, children hospital, Pakistan institute of medical sciences is not very effective as compared to developed countries, there is a need to improve the system and make provision of chelating agents in the center. Ferritin levels of the patients are much higher. Standard protocols of iron chelation therapy should be followed in order to have better results and so we can improve the life expectancy of the thalassemia patients.

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