
Original Article

A Report on Chelating Therapy and Patient Compliance by Determination of Serum Ferritin Levels in 243 Thalassemia Major Patients

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ABSTRACT

Background and Aim: This cross-sectional study was designed for determining the monthly serial serum ferritin levels and adequacy of Desferrioxamine usage in β -thalassemia major patients for roughly estimated outcome of compliance by subcutaneous Desferrioxamine chelation therapy.

Materials and Methods: In this study, 243 patients suffering from β -thalassemia major who had referred to the Thalassemia center affiliated to Ahwaz Jundishapur of Medical Sciences University, were investigated carefully and assessed for monthly serial serum ferritin levels. They received regular blood transfusions and follow ups were done in one year (Sept 1998 - Sept 1999). Ferritin levels were measured by IRMA technique. Patients with a high serum ferritin level due to false positive causes were excluded from this study. Iron chelating treatment was started when serum ferritin levels was about 1000-1500 $\mu\text{g/lit}$. This usually occurred after the first 10-20 transfusions (nearly 3 years of age). It was prescribed for regular daily adjusted dosage (subcutaneous, 25-50 mg/kg/24hr) over 8-12 hrs for administration at home. It was infused via a thin needle inserted subcutaneously and connected by an infusion line to a portable battery electrical infusion device. In selected heavily iron-load subjects, it was given via IV route in dose of 50 mg/kg/24hr, by short hospital admissions.

Results: Compliance adherence was observed only in 46 patients (18.2%, first group) with desirable serum ferritin levels less than 2000 $\mu\text{g/lit}$. Improved compliance adhesion was achieved in 78 patients (31.3%, second group) with unsatisfactory serum ferritin levels between 2000- 4000 $\mu\text{g/lit}$. Even though in this group the compliance adherence could be improved by close surveillance of Desferrioxamine infusions and intimate scrutiny by psychology intervention and social workers activity. In 119 patients (48.8%, third group) compliance was not achieved with serum ferritin levels more than 4000 $\mu\text{g/lit}$ and more. These high risk patients were kept under evaluation by medical care through IV Desferrioxamine infusion and other medical treatments as needed and collaboration of social worker and psychology intervention.

Conclusion: Compliance adherence was achieved only in 18.2% of patients (first group) and compliance adherence was improved by close surveillance of Desferrioxamine infusions and psychology intervention and social workers activity in 31.3% (second group). Despite every day encouragement, compliance was not achieved in 48.8% (third group). Overall outcome was poor.

Iranian J Pediatr Soc 2010; 2(2): 65-69

Keywords: Desferrioxamine, Major thalassemia, Serum ferritin

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Received: October 2009; **Accepted:** January 2010

INTRODUCTION

β -thalassemia is the most common genetic disorder in humans. Iran is one of the countries with a high frequency rate of 5-10% thalassemia gene distribution in the world (1). Khuzestan province in south-west of Iran includes a high frequency of thalassaemic patients (2).

Thalassemia is a well known disorder created by reduced production of β - globins chains that promotes RBC destruction. Patients are anemic and RBC stem cells in bone marrow are more active in a compensatory manner (3). In severe homozygous cases, erythropoiesis is dramatically accelerated; more than 95% of which may be ineffective due to toxic effects of excess α -globins chains which interfere with most stages of maturation. The RBCs are destroyed in bone marrow and ineffective erythropoiesis occurs resulting in significant erythroid marrow expansion (4), inappropriate skeletal developments, characteristic deformities of the skull and face, anemia and over absorption of iron from the small intestine.

Blood transfusion is necessary to preserve hemoglobin level more than 12 g/dl and prevent these malfunctions. Current recommendation favors transfusion regimens to maintain a pre transfusion hemoglobin level of 9-10.5 g/dl (5). In major thalassaemic patients each blood unit introduces 200-250 mg iron into the body and ferritin increases as an index of iron excess.

Desferrioxamine is used to decrease iron excess in this study; iron chelating treatment was to be started when serum ferritin levels reached 1000 -1500 $\mu\text{g/lit}$ which usually occurred after 10-20 transfusion (about 3 years). Desferrioxamine is infused via a thin needle inserted subcutaneously and connected by an infusion line to a portable battery electrical device. The infusion was continued for 8-10 hrs and was given 5-7 times per week at a mean daily dose 20-50 mg/kg body weight. The dose of Desferrioxamine was

adjusted according to body iron (serum ferritin level) and age (6).

MATERIALS AND METHODS

In this study, 243 patients suffering from β -thalassemia major who had referred to the Thalassemia center affiliated to Ahwaz Jundishapur University of Medical Sciences, where they were investigated carefully and assessed for monthly serial serum ferritin levels. They received regular blood transfusions and follow ups were done in one year (Sept 1998-Sept 1999). Patients were between 4-18 years of age with mean age of 11 ± 7 yrs. Ferritin levels were measured by IRMA technique. Patients with a high serum ferritin level due to false positive causes were excluded from this study.

Desferrioxamine with dosage of 25-50 mg/kg administered over 8 hrs was prescribed for administration at home; and in selected heavily iron-load subjects Desferrioxamine was given as IV with dosage of 50 mg/kg/24hr using short hospital admissions. Iron chelating treatment was started when serum ferritin levels reached about 1000 $\mu\text{g/lit}$ which usually occurred after the first 10-20 transfusions (about 3 years of age).

Desferrioxamine was infused via a thin needle inserted subcutaneously and connected by an infusion line to a portable battery electrical device. Five ml of distilled water was added to a bottle containing 500 mg of Desferrioxamine powder and shook well to make (10%) 5ml clear solution. The infusion was continued for 8-10 hrs and was given 5-7 times per week at a mean daily dose of 20-50 mg/kg body weight. The dose of Desferrioxamine was adjusted according to body iron (serum ferritin level) and age (5,6).

Dose adjustment was made with reference to the serum ferritin level using the therapeutic index (Porter JB. 1989); the aim was to keep the index 0.025 at all time (6).

Patients with hepatitis, inflammatory and infectious disease which induced high false serum ferritin levels, were excluded from the study. Laboratory Kit applied was Specteria Ferritin [125] which measured ferritin in a non-competitive Immunoradiometric Assay. Initially, monoclonal ferritin antibodies were added to the standard and serum samples. Then I₁₂₅ was banded to ferritin. Finally incubation was done and serum ferritin levels were determined by Gamma Counter.

RESULTS

Serum ferritin levels were measured in 243 patients, including 129 males (55%) and 114 females (45%). Serum ferritin levels in 46 patients (18.2%) were lower than 2000 $\mu\text{g/lit}$; so compliance was achieved only in 18.2% of the patients with desirable serum ferritin levels under 2000 $\mu\text{g/lit}$. Improved compliance was achieved in 33% (78 patients) with unsatisfactory serum ferritin levels between 2000-4000 $\mu\text{g/lit}$. Even though in this group the results could be improved by close surveillance of Desferrioxamine infusions and intimate scrutiny by psychology intervention and social workers activity. In 119 patients (48.8%) serum ferritin levels were more than 4000 $\mu\text{g/lit}$ (Table 1).

Despite every day encouragement in these patients, compliance was not achieved. These high risk patients were kept under evaluation by medical care via IV Desferrioxamine infusion and others medical treatments as needed along with the collaboration of social worker and psychology intervention. Overall outcome was poor.

DISCUSSION

Infusion of 20 units of packed RBCs induced 4 gr iron rise in serum that equals to total iron reservoir of an adult man. Normally there is no route for iron discharge.

Iron overload in major thalassemic patents results in cardiomyopathy, endocrine disturbance,

Table 1. Ferritin of 240 thalassemia patients using Desferrioxamine

Groups	Number of patients	Serum ferritin level $\mu\text{g/lit}$	Compliance
1	46	<2000 $\mu\text{g/lit}$	18.2%
2	78	2000-4000 $\mu\text{g/lit}$	32%
3	119	>4000 $\mu\text{g/lit}$	48.8%

hepatomegaly, splenomegaly and metabolic disorder such as disorders of growth and development, delayed puberty, hypothyroidism and hypoparathyroidism, and pancreatic insufficiency (diabetes mellitus). Free radicals are formed consequent to iron overload and could be harmful to lipids, proteins and DNA (4).

Serum ferritin, as an index of total body iron, should be measured periodically. Normal serum ferritin level in male is 15-200 $\mu\text{g/lit}$ and in female is 12-150 $\mu\text{g/lit}$.

Desferrioxamine, as iron chelating agent, with dose of 25-50 mg/kg/day is used to prevent iron overload and its harmful effects. Optimum serum ferritin level in major β -thalassemic patients is 1000-1500 $\mu\text{g/lit}$. Daily subcutaneous injection of Desferrioxamine is used to improve the patients and their surveillance (4). There is 100% surveillance in well treated patients with Desferrioxamine vs. 32% surveillance in poor treated patients with Desferrioxamine (7-9). Anesthetics such as AMLA ointment used at the infusion site and supporting the patients make treatment more acceptable and better results could be acquired (9).

Desferrioxamine side effects consist of nyctalopia (night blindness, imperfection of vision at night) and deafness. These side effects are more reported in renal insufficiency; so renal function tests should be done periodically specially in venous infusion.

Desferrioxamine intoxicity occurs in over 60 mg/kg dosage. In patients with serum ferritin levels less than 1000 gr/lit due to Desferrioxamine over dosage, short stature involving the trunk, wrist and knees may occur. Genu valgum and

flattening of vertebrae are also probable (4). Despite prescribing and delivering enough Desferrioxamine to the patients in this study, iron overload was observed due to irregular or insufficient usage of Desferrioxamine by most of patients.

Overall, serum ferritin levels were measured in 243 patients as an index of total body iron ranging from 1000- to >10,000 $\mu\text{g/lit}$ or more. In the first group serum ferritin levels in 46 patients (18.2%, first group) was lower than 2000 $\mu\text{g/lit}$ and compliance was achieved. Serum ferritin levels in (33%) of patients (second groups) were between 2000-4000 $\mu\text{g/lit}$. It is not desirable, but better compliance outcome was achieved if Desferrioxamine usage was adjusted by physician with collaboration of social workers and psychology intervention. In the third group (48.8%), patients' serum ferritin levels remained over 4000 $\mu\text{g/lit}$ to an upper ranges of 10,000 $\mu\text{g/lit}$ or more. Despite repeated everyday encouragement, compliance was not achieved with serum ferritin levels more than 4000 $\mu\text{g/lit}$ and more. These high risk patients were kept under evaluation by medical care via IV Desferrioxamine infusion and others medical treatments as needed and collaboration of social worker and psychology intervention. Overall, treatment outcome was poor.

Experience with chronic diseases such as diabetes, renal failure and hypertension, *etc.* indicate that adherence to treatment averages (40 - 60%) (9). Factors consistently associated with poor adherence in chronic diseases include (9,10):

- * Lack of knowledge about the disease
- * Lack of awareness of the reasons for medication
- * Anxiety about taking medication
- * Concern of fear about side effects
- * Health beliefs
- * Complexity of regimen
- * Poor doctor-patient relationships

All of these factors indicate that one of the primary goals of psychological support is to ensure the patients and provide them with all the

information they need to know about their disease (11).

In face to face talking with most of the patients in the third group (with inadequate Desferrioxamine usage and poor compliance) we found inability to read, write and talk in Persian (12) in both parents and patients were confused, misunderstood and made important mistakes in their relationship with the physicians (11).

Ignorance in regards to inappropriate usage of Desferrioxamine and others medications is based on poor socio-economical factors, coming from rural area (11,12), thalassemia center located far from home, very hot climate in the summer, and fear of daily Desferrioxamine injection and infusion by both parents and patients (11).

These patients essentially need prompt social worker communication help and psychological intervention not only for Desferrioxamine injection and hospital admission, but also for low family income (they have excellent charity insurance and all hostelling in hospital and other services with no payment); although it is not enough. They need transportation, home care, nutrition, *etc* (12). Other important factor was bilingualism (Persian-Arabic) in the region.

CONCLUSION

For better relationship for intervention of the patients, physician and social workers facilitated set up by employing bilingual secretaries and social workers is required. There are also current consanguine marriages with no family planning in this ethnic group population. Thus, there is need to establish a family planning center next to the Thalassemia clinic with supervision of a midwife under control of Ministry of Public Health Services affiliated to Ahwaz Jundishapur University of Medical Science for teaching family planning program to those who need these services (13,14).

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