International Journal of Pathology; 2004; 2(2):71-74

Ferritin Levels in Patients of Beta Thalassaemia Major

Nadeem Ikram*, Khalid Hassan, Muhammad Younas**, Samina Amanat***

* District Head Quarters Hospital, Rawalpindi
** Pakistan Institute of Medical Sciences, Islamabad

In Beta Thalassaemia Major repeated blood transfusions, ineffective erythropoiesis and increased gastrointestinal iron absorption lead to iron overload in the body. 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 the present study serum ferritin levels, of the patients with beta thalassaemia major registered at two different centers of Rawalpindi and Islamabad, were measured. Majority of the patients revealed very high ferritin levels, with a mean of 3390 ng/ml. 21.34% patients had serum ferritin between 1000 to 2500 ng/ml, while 76% patients had values above 2500 ng/ml. These levels reflect inadequate chelation and vulnerability to develop iron overload related complications. There is a dire need to rationalize the chelation therapy, as at present no chelation, inadequate chelation, improper methods of chelators administration, non availability of infusion pumps, non affordability of patients to purchase pumps and chelators, inappropriate evaluation of iron overload and high levels of serum ferritin gives an overall bleak view.

Key words: Beta Thalasaemia major; Ferritin; iron chelators …….

Introduction

Thalassaemia will remain to be the one of the major health problem for at least the next few decades, particularly in developing countries. Although the survival of thalassaemics is steadily increasing, the prevalence of complications due to iron over load remains high. Iron overload is the life limiting complication commonly found in thalassaemics.[1] The progressive iron overload in Beta thlalssaemia major patients is the consequence of ineffective erythropoiesis, increased gastrointestinal absorption of iron, lack of physiologic mechanism for excreting excess iron, and above all multiple blood transfusions. A unit of red blood cells transfused contains approximately 250 mg of iron, while the body can not excrete more than 1 mg of iron per day. The iron which exceeds the iron binding capacity of transferrin appears in the plasma as non-transferrin bound iron, which is highly toxic to tissues.[2] The accumulation of iron results in progressive dysfunction of the heart, liver and endocrine glands. The iron burden on the body can be estimated by means of serum ferritin, iron and TIBC levels. Hepatic iron levels can be evaluated by liver biopsy, Magnetic Resonance Imaging(MRI) and magnetic susceptometry. The assessment of heart damage due to iron overload can be assessed clinically as well as by Chest X- ray, ECG, assessment of $T2^{*}$ by MRI, ECHO, radionucleide (MUGA) scan to check left ventricular ejection fraction. The assessment of tissue damage, due to iron overload, in endocrine organs can be made by clinical evaluation of growth and sexual development, glucose tolerance test, pituitary gonadotrophin release test, thyroid, parathyroid, gonadal, adrenal functions, growth hormone assay and X- rays for bone size.[3, 4] The estimation of serum ferritin levels is the most commonly employed test to evaluate iron overload in Beta Thalassaemia Major. The association between serum ferritin and levels of body iron are well established and the test is easy to perform compared with other tests for iron overload.[5] When the serum ferritin level reaches at 1000 ng/l (usually after 10th to 12th transfusion), it is generally taken as the point to initiate iron chelation therapy. The most commonly used agent for iron chelation is Deferioxamine, a naturally occurring siderophore produced and purified from microbe Streptomyces pilosus. A regime of 40 mg/kg (range 30 – 50 mg/kg) is given as 8 – 10 hours subcutaneous infusion on a minimum of five nights a week. One molecule of chelator binds one atom of iron forming a highly stable hexadentate iron complex ferioxamine at physiologic pH. An oral agent Deferiprone (L1), administered in a dose of 75 mg/kg/day, is also available. But its efficacy and toxicity profile are undetermined.[6]

Patients and Methods

Patient's selection: A total of 75 cases of β - thalassaemia major were included in this prospective study. This study was conducted at Thalassaemia Management Center, Holy Family Hospital, Rawalpindi and department of Pathology, Pakistan Institute of medical Sciences , Islamabad, from July to September 2003. The patients registered for transfusion at these centers were randomly selected.

Known cases of β - thalassaemia major that had been transfused at least ten units of blood, irrespective of their age and sex were included in this study. Patients who had been transfused less than 10 units of blood as part of their management were excluded.

Clinical Account: The clinical details of patients were recorded in a performa, taking into account the age, frequency of transfusions, awareness about estimation of serum ferritin levels and ill effects of iron overload. The record of iron chelation therapy, i.e., days of week in which patients received chelation, route of administration and availability of infusion pumps was also obtained.

Serum Ferritin Estimation: About 3 ml of patient's blood sample was collected by a clean venepuncture. The blood was allowed to clot. Serum was separated and stored at –20^{0}C. Ferritin levels were performed by ELISA, in batches of ten each, alongwith normal and abnormal controls.

Results

In a total of 75 cases of thalassaemia major studied in this series, 48 were males and 27 females with a male to female ratio of 1.77: 1. The age of patients at the time of diagnosis ranged from 6 months to 2 ½ years with a mean of 1 year and 4 months. The age at the time of this study ranged between 2 years 5 months and 21 years.

The interval between successive transfusions varied between 7 days and to 5 weeks in different patients. In 54 patients(72%), the frequency of transfusion had gradually increased.

More than half (54.7%) the patients were not confined to one center and they reported to different centers for blood transfusions, while 45.3% patients were found to get their transfusions from one center.

At one center the patients were being given iron chelator (deferioxamine) only at the time of blood transfusion in the form of bolus infusion while at the other center the patients were being offered iron chelator subcutaneously, but the days of weeks and the duration of administration were found to be highly variable. Fifty five patients (73.3%) did not get any type of iron chelators.

Serum Ferritin Levels: The mean serum ferritin levels were 3390 $\pm$ 135.6 ng/ml. Only two patients(2.67%) had serum ferritin levels of less than 1000 ng/ml. Sixteen patients(21.34%) had serum ferritin levels between 1000 – 2500 ng/ml, while 57 patients (76%) had values more than 2500 ng/ml.(Table 1)

Table 1: Serum Ferritin in Patients with Beta Thalassaemia Major

Levels	Number of patients
< 1000 ng /ml	2 (2.67%)
1000 – 2500 ng/ml	16 (21.34%)
>2500 ng/ml	57(76%)

Discussion

The practical management of iron overload requires reliable estimation of body iron content and distribution as well as understanding of how iron overload translates into clinical consequences. The ability to estimate the distribution of excess iron, to predict its consequences and therefore to tailor treatment accordingly is surprisingly imprecise. The understanding of how iron chelators prevent these consequences is also limited. Beta Thalassaemia Major patients in our set up are facing all the problems associated with iron overload, improper chelation and transfusion associated infections. In the present study majority of the patients showed very high serum ferritin levels(Table 1) . Certain pervious studies have shown that in our part of world patients with beta thalassaemia major have levels of serum ferritin far more than the patients in developed countries (Table 2). In our set up only a few patients get their serum ferritin levels done once a year. An occasional patient has his own infusion pump. The chelation therapy is not standardized. Some are receiving Deferoxamine in the form of intravenous bolus at the time of transfusion and some receive chelation therapy, through infusion pumps, a few days a month. Studies revealed that large intermittent doses of chelator will be less efficient and potentially more toxic than lower doses given more continuously.[5]

The goals of transfusion include correction of anaemia, suppression of erythropoiesis and inhibition of increased gastrointestinal absorption of iron. For patients of beta thalassaemia major different transfusion protocols are suggested. In our setup the patients reports to blood centers for blood transfusion in a haphazard manner. "Hypertransfusion" and " Supertransfusion" regimens achieve the goals of anaemia correction and suppression of erythropoiesis but are associated with substantial iron loading. These regimens have been supplanted by regimens in which heamoglobin concentration before transfusion does not exceed 9.5 gram per deciliter. These newer regimens are associated with both adequate marrow suppression and relatively lower rates of iron accumulation.[9, 10]

Table 2: Comparative Serum Ferritin Levels

Study	Serum Ferritin levels (mean) Reference Range : Male : 20 – 300 ng/ml Female: 15 – 120 ng/ml
Ayidno KY et al, 2002[7]	1931 ng/ml
Cunningham MJ et al, 2004[8]	1696 ng/ml
Rehman M, 2004[9]	2861 ng/ml
Choudhry VP,et al, 2004[13]	6723 ng/ml
Present study	3390 ng/ml

In patients who are not receiving transfusions, abnormally regulated iron absorption results in increases in body iron burden ranging from 2 to 5 grams per year, depending on the severity of erythroid expansion. Regular transfusions may double this rate of iron accumulation. Although most clinical manifestations of iron loading do not appear until the second decade of life in patients with inadequate chelation, evidence from serial liver biopsies in very young patients indicates that the deleterious effects of iron are initiated much earlier than this. After approximately one year of transfusions iron begins to be deposited in parenchymal tissues, where it may cause substantial toxicity as compared with that within reticuloendothelial cells. As iron loading progresses the capacity of serum transferrin, the main transport protein of iron, to bind and detoxify iron may be exceeded and a non –transferrin - bound fraction of plasma iron may promote the generation of free hydroxyl radicals, propagators of oxygen – related damage.[11, 12]

In the absence of or due to inadequate chelation therapy the accumulation of iron results in progressive dysfunction of the heart, liver and endocrine glands. Within the heart, changes associated with chronic anaemia are usually present in patients who are not receiving transfusions and are aggravated by iron deposition. Extensive iron deposits are associated with cardiac hypertrophy and dilatation, degeneration of myocardial fibres, and in rare cases fibrosis. The survival of patients with β thalassaemia is determined by the magnitude of iron loading within the heart. Iron induced hepatic fibrosis and cirrhosis can be seen in many patients. Iron loading within anterior pituitary is the primary cause of disturbed sexual maturation and secondary amenorrhea. Diabetes mellitus is seen in 5% of adults. Over the long term iron deposition also damages thyroid, parathyroid and adrenal glands. In most studies bone density is markedly reduced in patients with β thalassaemia.[11] In our set up almost all patients show some level of growth impairment as is evident from their weight and heights.[9]

The iron status of the body in overload conditions can be assessed by different methods. 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. Estimation of direct liver iron concentration is the most accurate method of estimation of iron overload. But in our set up this facility is not available. Although heart failure is the main cause of death in iron overload , the uneven distribution of iron in heart tissue, impracticability of obtaining an endomyocardial biopsy , and non availability of MR T2¨ makes the assessment of cardiac iron virtually impossible . Serum ferritin measured at regular intervals (at least 3 months) has some therapeutic and prognostic use. A target ferritin of approximately 1000 ng/l is generally recommended standard practice in thalassaemia major and the patients having values below 2500 ng/l on two thirds

of occasions had less risk of cardiac complications than patients who failed this achievement.[5]

The management of iron overload is usually tailored according to individual in question. The treatment and diagnostic tools currently available have a number of limitations. The efficacy of currently used chelation regimens is remarkably low. Ninety percent of administered deferioxamine is excreted without binding iron with 96% of deferiprone (L1) having the same fate.[14] As, thalassaemia is primarily a problem of developing countries, the drugs used for the treatment of iron overload and the patients with iron overload are facing the paucity of large controlled prospective studies . The governmental bodies and pharmaceutical companies should address this issue.

Blood transfusion and iron chelation remain the cornerstone of treatment for patients with β - thalassaemia major. However, this therapy is costly, burdensome, not curative, and compromised by non-compliance . New therapeutic solutions are needed for patients in both developing and developed countries. Novel ways of using deferioxamine, new oral iron chelators(defriprone, ICL – 670) and combination therapy are the hope for the immediate future. Although still not curative , these therapeutic options have the potential to improve effectiveness and compliance, while reducing the risk of toxicity. Stem cell or allogeneic marrow transplant is curative for this disorder . But its exuberant expenses, associated morbidity and mortality , and giving credence to serum ferritin levels and other complications, majority of our patients appear as unfit candidate for this modality. The availability of more treatment choices will permit better individualization of therapy and protection from iron overload.[2, 15]

References

1. Wangruangsattit S, Hathirat P, Chuansumrit A, pakakasama S, Hongeng S. The correlation of transferrin saturation and ferritin in non- splenectomized thalasemic children. J Med Assoc Thai, 1999; 82(1) 74 – 76.
2. Giardina PJ and grady RW. Chelation therapy in β- thalassemia ; An Optimistic Upate. Hematol, 2001, 38: 360 –366.
3. Midiri M, Locasto A, Sparacia G, et al. MRI imaging of pancreatic changes in patients with transfusion dependent beta thalassaemia major. Am J Roentgenol, 1999; 173(1): 187 – 192
4. Soliman AT, Elzalabany M, Amer M, Ansari BM. Growth and pubertal development in transfusion dependent children and adolescents with thalassaemia major and sickle cell disease; a comparative study . J Trop Pediatr, 1999; 45(1): 23 - 30.
5. Porter JB. Practical management of iron overload. British Journal of haematology, 2001; 115: 239 – 253.
6. Hoffbrand AV, Cohen A, Hershko C. Role of deferiprone in chelation therapy therapy for transfusional iron overload. Blood, 2003; (102): 17 – 22.
7. Aydino KY, Darcan S, Polat A, et al. Endocrine complications in patients with beta thalassaemia major. Journal of Tropical Paediatric, 2002; 48(1): 50 – 54
8. Cunningham MJ, Mackin EA, Nenfeld EJ, et al. Complications of beta thalassemia major in North America. Blood , 2004; 104(1); 34 – 39
9. Rehman M and Lodhi Y. Prospects and future of conservative management of beta thalassaemia major in a developing country. Pak J Med Sci, 2004; 20(2): 105 - 112
10. Thalassemia International Federation ; Guidelines for the clinical management of thalassemia. Nicosia, Cyprus, TIF,2000.
11. Oliveri NF. The β- thalassemias. New Eng J of Med, 1999; 341: 99 – 107
12. Laksmitawati DR, Handayani S, Udyaningsih FSK. Iron status and oxidative stress in beta thalassaemia patients in Jakarta . Biofactor, 2003; 19(1-20: 53 – 62.
13. Choudhry VP, Patitt P, Saxena A, Maiaviya AN. Deferiprone , efficacy and safety . Indian J Pediatr , 2004; 71(3): 213 – 216.
14. Al Rafaie EN, Hershko C, Hoffbrand AV, et al. Result of long term Deferiprone (L1) therapy : a report by the international study group on Oral Iron chelation. British Journal of Haematology, 1995; 91: 224 – 229)
15. D' Angelo E, Mirra N, Rocca A, Carnelli V. Combined therapy with desferrioxamine and deferiprone : a new protocol for iron chelation in thalassaemia . J Pediatr Haematol Oncol, 2004; 2697): 451 – 453.