

## ROLE OF CHELATING AGENTS IN THALASSAEMIA MAJOR PATIENTS

G. ALI SIRHINDI, S. SHAHID ALI

*Departments of Pathology and Zoology, Shaikh Zayed Hospital and University of the Punjab, Lahore*

### ABSTRACT

*The purpose of this work was to evaluate current chelation in thalassaemia major patients. It is a retrospective study. This study was conducted at a charity blood transfusion center in Lahore; from March 2006 to August 2006. One hundred and seventy patients suffering from transfusion dependent thalassaemia major were evaluated for chelation practice and iron overload. Among them 98.2% were found to be either non-chelators or inadequate chelators whereas 82.3% patients had serum ferritin levels above 2500 ng/ml. Growth failure and hepatosplenomegaly were also common. Survival appears to be limited as only 6 patients were older than 20 years. Patients face risks and complications during treatment of thalassaemia major. Urgent and effective measures need be taken to remove the difficulties to improve quality of life in these patients. Involvement of clinical haematologists or physicians in the treatment of thalassaemia major can produce promising results.*

### INTRODUCTION

Iron overload can be fatal as its tissue accumulation can result in progressive dysfunction of the heart, liver and endocrine organs.<sup>1</sup> In patients receiving transfusion but not chelation therapy, symptomatic cardiac disease has been reported within 10 years of the start of transfusion.<sup>2</sup> Hepatic fibrosis, if not prevented by effective iron chelation, may also progress to cirrhosis in the first decade of life.<sup>3</sup> Regular red blood cell (RBC) transfusions eliminate the complications of anaemia, compensatory bone marrow expansion, permit normal growth throughout childhood, and extend survival. The most important consequence of these life saving transfusions is the inexorable accumulation of iron within tissues.<sup>4</sup> Stunted growth, delayed puberty, hypothyroidism and diabetes mellitus are well-recognized complications of iron overload. Thus iron overload constitutes the most important complication in thalassaemia major and is the major focus of clinical management.<sup>5</sup>

Effective chelation reduces or prevents iron accumulation and iron-mediated organ damage, resulting in a consistent decrease of morbidity and mortality. Today, in the developed world, the life expectancy of patients with thalassaemia varies between 25 and 55 years, mainly depending on compliance with medical treatment. Though a new iron chelator deferasirox (ICL 670) has been approved by US Federal Drug Administration in 2005, and deferiprone (L1) is commercially available in India and Europe for the last 10 years, desferrioxamine remains the only iron chelating agent having overwhelming evidence on its safety and efficacy.<sup>6,7</sup> Poor compliance with chelation regi-

mens is common even in countries where standard recommended treatment is available and affordable. This constitutes the most important threat to the occurrence of complications leading to increased morbidity and mortality in these patients. Patients who administer subcutaneous desferrioxamine infusion about five times a week (250 times a year) have 95% survival to 30 years of age, whereas survival is only 12% in patients who fail to achieve this target.<sup>8</sup>

Current practice is to begin iron chelation with desferrioxamine when the serum ferritin levels reach 1000 ng/ml or when child reaches three years of age or has received about 10-20 transfusions. To be effective, treatment should be an 8-12 hour subcutaneous infusion 7 days a week, with a minimum of 5 days a week; frequencies less than this would lead to significantly shorter survival. The dose of desferrioxamine should be adjusted according to the body iron stores and age.<sup>9-10</sup>

The present study was conducted to evaluate the current chelation practices in thalassaemics in our setup and to estimate the iron overload.

### PATIENTS AND METHODS

We evaluated one hundred and seventy patients of thalassaemia major at the specialist clinic Sundus Foundation, Shadman, Lahore over a period of six months (March 2006 to August 2006). Ages of patients ranged from 3-28 years. They had received more than 20 transfusions. Record of chelation treatment was available. Information was also obtained through an interview by doctor. The patients included in this study had transfusion dependent thalassaemia and they were three years old or

more. Parents, and in a few cases patients were questioned in detail about the age at the beginning of transfusion, number of transfusions received, prescription and explanation of iron chelation, age at the beginning of iron chelation, type of chelating agent used, dose and route of administration, frequency per week, evaluation for iron overload/measurement of serum ferritin levels and adjustment of dose of desferrioxamine/ deferiprone according to changes in ferritin levels and weight of the patient; information about the problems of using desferrioxamine/deferiprone and adverse effects were also obtained. Heights and weights of patients were measured and plotted on centile chart. Liver and splenic sizes were also measured (in cms) below right and left costal margins respectively. A sample of 5 ml venous blood without frothing was obtained from patients and allowed to clot. Serum was separated and stored in a freezer for measurement of serum ferritin levels.

## RESULTS

One hundred and seventy patients with transfusion dependant thalassaemia were evaluated. Of these, 100 were boys and 70 were girls. Their age ranged from 3 to 28 years. Forty patients were aged 5 years or less, 80 were between 6-10 years, 30 between 11-15 years, 14 between 16-20 years, 5 between 21-25 years and only one patient was 28 years. Growth failure and organomegaly were also common. Liver was enlarged more than 2 cms in 162 and more than 5 cms in 8 patients. Spleen was enlarged more than 6 cms in 70 patients, less than 6 cms in 92 and not palpable in 8 patients.

**Table 1:** Serum ferritin levels.

Serum ferritin level (ng/ml)	Number	Percentage
< 1000	1	0.58
1000 – 2500	29	18.07
> 2500	140	81.35

Only three patients were being chelated regularly. The remaining 167 (98.2%) were either non-chelators or inadequately chelated. Sixty patients or their parents had no idea of iron overload, its consequences and need for iron chelation treatment. They had never used desferrioxamine or deferiprone. One hundred and twelve patients (65.8%) were inadequate chelators. They were familiar with the development of iron overload and its consequences, but knowledge regarding the need and benefits of regular iron chelation was grossly inadequate. They had used less than the required number of doses and the amount of burden.

Almost all of them had used desferrioxamine intermittently and some had even discontinued for variable reasons. The dose of desferrioxamine had not been regularly adjusted regularly according to changes in serum ferritin levels or changes in body weight. Ten patients used deferiprone for a period of 1-9 years. One patient discontinued deferiprone due to development of severe neutropaenia. Another temporarily stopped using deferiprone due to neutropaenia. Two more patients discontinued due to bitter taste of the medication. Iron overload is estimated by measurement of serum ferritin levels. Serum ferritin levels were less than 1000 ng/ml in only one patient, between 1000-2500 ng/ml in 29 patients, and above 2500 ng/ml in 140 patients.

## DISCUSSION

Regular use of desferrioxamine has been found to deliver an impressive reduction in the prevalence and severity of complications due to iron overload. Over recent years there has also been remarkable progress in the development of oral iron chelators. According to them chelation is an essential part of standard treatment of thalassaemia.<sup>6</sup>

It is clear from the results of the current study that 167 patients (98.2%) did not receive iron chelation as a part of standard treatment of thalassaemia as they were either non-chelators or ineffective chelators. Sixty (35.2%) patients had no idea of development of iron overload. A total of 112 (65.8%) patients used desferrioxamine and/or deferiprone but the compliance was so inadequate that iron chelation was more or less ineffective in controlling the iron burden. Almost all of them had late start of chelation therapy. Most of them used desferrioxamine with frequent discontinuation and even with regular use, the frequency was less than five doses per week. The dose of chelating agent was not regularly adjusted according to changes in the body weight or changes in serum ferritin levels.

It has been observed that nearly all patients had lapses in their adherence to iron chelation therapy, as the efficacy of this treatment is not readily apparent.<sup>11</sup> In Egypt, India and Iran, nearly half the patients were using desferrioxamine three days or less each week.<sup>12</sup> Problem of compliance is more common and severe in countries where comprehensive treatment is not available to the majority of thalassaemics.<sup>13</sup> Patients receiving regular blood transfusions and less than two thirds of the recommended desferrioxamine doses are known to have increased risk of complications later in life as a result of iron accumulation. Ineffective chelation therapy was associated with greatest risk of complications in thalassaemia major, and the proba-

bility of survival to the age of 25 years was only 32% among the ineffective chelators.<sup>7</sup> Most of the patients in this study developed severe iron overload as indicated by markedly raised serum ferritin levels. Serum ferritin levels were above 2500 ng/ml in 140 (82.3%) patients, thus exposing them to serious risk of developing multiple, life threatening complications.<sup>14</sup>

A possible explanation for these markedly raised serum ferritin levels is the complex pathogenesis of iron overload in our patients, whose transfusion is irregular. These patients with persistently low haemoglobin levels and consequent development of hypersplenism in the long run have high requirement of red cells, thus resulting in a higher ultimate iron burden. On the other hand, when haemoglobin is low, patient's own ineffective erythropoiesis is hyperactive resulting into higher gastrointestinal iron absorption. Enlargement of liver is another common observation. These patients who have enlargement of liver and severe iron overload are also likely to have marked hepatic fibrosis or cirrhosis.<sup>7</sup>

Growth failure is also common. This phenomenon is more common and more marked in older patients. This is comparable to other studies from the developing countries. Possible reasons are persistent anemia due to inadequate transfusion and complication of iron overload.<sup>15</sup>

In our patients survival appears to be limited, as a few patients are alive after 20 years of age. There is a rapid drop in number of patients older than 15 years; five patients were older than 20 years and only one patient was 28 years old. This finding is in contrast with the current outlook and quality of life in countries where comprehensive treatment is available, but is typical of a developing country scenario where most patients have limited survival with death usually occurring in adolescence or early adulthood. In developed countries the life expectancy of patients with thalassaemia major varies between 25-55 years, mainly depending on compliance with the medical treatment.<sup>16</sup>

### CONCLUSION AND SUGGESTIONS

Iron chelation is a neglected component of treatment of thalassaemia major in our country. Our findings show the risks facing our patients in terms of survival and complications. There is a need for an action and effective measures to identify and remove the obstacles. Moreover the social welfare organizations, focus on quality of treat-

ment and involvement of physicians familiar with the current concepts in management of thalassaemia can produce quick results.

### ACKNOWLEDGEMENTS

The authors are thankful to the Sundus Foundation, Lahore for providing the facility to go through their data.

### REFERENCES

1. Taher A. Iron overload in thalassaemia and sickle cell disease in Novel Approaches in the Treatment of Overload. *Seminars in Haematol* 2005; 42: 55-59.
2. Agarwal MB. Advances in management of thalassaemia. *Ind Paediatrics* 2004; 41: 989-92.
3. Oliveri NF. The  $\alpha$ -thalassaemia. *N Eng J Med* 1999; 34: 99-109.
4. Oliven NF, Britterham GM. Iron chelating therapy and the treatment of thalassaemia. *Blood* 1997; 89: 739-61.
5. Cunningham MJ, Macklin Ea, Neufeld EJ, Cohen AR. Complications of  $\alpha$ -thalassaemia major in North America. *Blood* 2004; 34-39.
6. Neufeld EJ. Oral chelators deferasirox and deferriprone for translusional iron overload in thalassaemia major: new data, new questions. *Blood* 2006; 107: 3436-41.
7. Brittenham GM, Griffith PM. Efficacy of desferrioxamine in preventing complications of iron overload in patients with thalassaemia major. *N Eng J Med* 1994; 331: 567-73.
8. Gabutti V, Piga A. Results of long term chelation therapy. *Acta Haematol* 1996; 95: 26-36.
9. Porter JB. Practical management of iron overload. *Br J Haematol* 2001; 115: 239-53.
10. Hershko C. Role of iron chelation therapy in thalassaemia major. *Turk J Haematol* 2002; 19: 121-26.
11. Eleftheriou A. Copliance to iron chelation therapy with desferrioxamine. *Thalassaemia International Federation*, 2000.
12. Ward A, Caro JJ, Green TC, et al. An international survey of patients with thalassaemia major and their views about sustaining life long desferrioxamine use. *Bone Clin Pharmacol* 2002; 2-3.
13. Angistiniolis M. Why prevention. In: *Prevention of thalassaemias and other Haemoglobin Disorders*. Thalassaemia International Federation, 2003.
14. Rund D, Rachmilewitz E. Beta thalassaemia. *N Eng J Med* 2005; 353: 1135-46.
15. Kwan EYW, Lee ACW, Li AMC, et al. A cross-sectional study of growth, puberty and endocrine function in patients with thalassaemia major in Hong Kong. *J Pediatr Child Health* 1995; 31: 83-87.
16. Low LCK. Growth of children with  $\alpha$ -thalassaemia major. *Ind J Pediatr* 2005; 72: 159-64.