Effect of Oral Iron Chelator Deferiprone on Skeletal Radiography of Thalassemia Major Patients

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Abstract

Regular blood transfusion along with iron chelation therapy is a supportive treatment for thalassemia major. Chelation therapy too has its side effects. The most common adverse effects associated with administration of deferiprone are agranulocytosis, neutropenia and arthralgia, primarily, of the large joints. Objective : The study was undertaken to examine the effect of deferiprone on the large bone joints of thalassemia major patients. Material and Methods: Thalassemia major patients (62) on hyper-transfusion treatment regime aged between 4 19 years were assigned to three groups. Group I included 42 patient taking deferiprone, Group II included 10 patients on deferoxamine, and Group III included 10 patients who were not taking chelation therapy.

Index terms— Thalassemia, iron chelation, deferoxamine, bdeferiprone, musculo-skeleton.

1 I. Introduction

-thalassaemia major is the commonest lethal single gene disorder in India with a prevalence of 1-17% in different population groups (mean prevalence is 3.3%). This disease has a spectrum of clinical severity which is associated with ineffective erythropoeisis, bone marrow expansion and repaid destruction of erythrocytes.

Anemia demands frequent blood transfusion to maintain life while hemosiderosis and other complications of the disease require a continuous and distressing treatment regime that includes iron chelation treatment regular medical supervision, request admissions to the hospital and on many occasions Authors ? : MD, PhD, PhD (Cantab) Associate Professor, Department of Nephrology. Author ? : MD, Additional Professor Department of Radiodiagnosis Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow 260014, India. E-mail : anitimmy@sgpgi.ac.in. anemia, caused by abnormality of beta globin synthesis, is fatal in infancy without transfusions but is fatal in adolescence even with them.

The only curative treatment for this disease is bone marrow transplantation (BMT) which is expensive, not easily affordable by a common Indian family and with variable success rate of BMT 60-70%.

Regular blood transfusion followed by iron chelation therapy is just a supportive treatment for this disease which is associated with serious complications. The cost of supporting a thalasemic child varies from few thousand rupees to Rs.1,00,000 a years depending upon the kind of treatment opted by the family. The excess iron causes diffuse organ damage, usually resulting in fatal cardiac toxicity.

In supportive treatment, because the magnitude of the body iron burden seems to be the principal determinant of clinical outcome [2][3][4] the prime goal of iron-chelating therapy in patents with thalassemia major is to control iron overload. The optimal body iron should minimize both the risk of adverse effects from the iron-chelating agent and the risk of complications from iron overload. With stable transfusion requirements and in the absence of other confounding factors, the lower the level of body iron is desired, the higher the dose of iron chelator is required., The advent of treatment with subcutaneous deferoxamine has, however, changed the gloomy prognosis of the disease. Studies have demonstrated that over 90% of patients who comply with the difficult and expensive regimen of deferoxamine treatment survive without heart disease **??**.5 and with minimal toxic effects

(deferoxamine induced bony changes are well documented [6][7][8][9][10]) if dose is tailored to the iron burden 11 .

The successes achieved with deferoxamine, as well as the limitations of this treatment, have stimulated the design of alternative strategies of iron chelating therapy, including orally active iron chelators. Only a few of the many hundreds of potentially useful oral chelators have been found suitable for clinical studies. The development of the most promising of these deferiprone (1, 2 dimethy 1-3-hydroxypryridin-4-one or LI) has progressed rapidly and data from several trails have provided direct and supportive evidence for its short-term efficacy 12 . Deferiprone is able to promote this agent mandates a careful evaluation of the balance between risk and benefit of deferiprone in patients with thalassemia in most of whom long-term deferoxamine is safe and efficacious therapy. The most common adverse effect associated with administration of deferiprone has been arthralgias, primarily, of the large joints **??**13,[15][16][17][18] the etiology of which remains elusive bringing into question its long term use in humans 19 , neutropenia or agranulocytosis first reported in 1989 20 . This study was undertaken to examine the effect of deferiprone on the large bone joints of thalassemia major patients.

2 II. Material and Methods

The study was conducted at Sanjay Gandhi Post Graduate Institute of Medical Sciences, Luckknow between year 2001 and year 2002 on 62 thalassemia major patients on hyper-transfusion treatment regime aged between 4 and 19 years registered with department of Medical Genetics. The patients visited hospital every 3 to 4 weeks for blood transfusion. Patients were divided into three groups based on which chelation therapy they were taking. Group I included 42 patients taking deferiprone (duration 6 months to 6 years), Patients in Group II were on deferoxamine infusion and belonged to rich Indian class who could afford good and expensive treatment.

Group III included 10 patients who were not taking chelation therapy because of financial constraints. Patients from Group I and III belonged to low and middle socioeconomic groups who could not afford expensive treatment.

Clinical history of the patient is given in Table **??**. Prior to starting deferiprone or deferoxamine complete blood count (CBC), serum ferritin, ,liver function test (serum bilirubin, AST, ALT, serum alkaline phosphate), HIV I & II antibodies, and blood sugar fasting and post meal were tested. All the patient were immunized for hepatitis B. Growth assessment of the patients was done once in three months.

Routine Tests : Pre-transfusion hemoglobin was tested on every visit and serum ferritin levels every six months. Yearly evaluation of endocrine glands included TSH, T4, serum Cortisol, GTT, Calcium and Phosphorus.

Deferiprone : Patients were given deferiprone after written consent had been obtained from their parents. The parents were given detailed information on efficacy, safety and potential side effects of deferiprone (marketed in India as Kelfer, Cipla Ltd.). Dose was prescribed as follows: starting dose 50 mg/kg body weight, which was gradually increased ton 60 mg, 75mg and finally to 1000 mg/kg body weight. CBC was checked every month. Deferiprone was discontinued if patient developed high fever, prolonged or abnormal bleeding, or if total leucocyte count was <4000/I or platelets <1000,0001/1. Deferiprone was stopped in case patient developed bone joint related problems. The patient was then managed on non-steroidal antiinflammatory drugs. After the symptoms resolved, the drug was restarted.

Deferoxamine : Starting dose of deferoxamine was 25 mg/kg body weight which was gradually increased up to 45 mg/kg body weight. Patients on this drugs were advised to take Vitamin C on the day of infusion.

Radiograph : To examine bone age, bone density, bone expansion, peri-articular changes (arthritic changes, soft tissue swelling, loose bodies and reduction in joint space) antero-posterior and lateral views of wrist, knee and ankle joints were taken and analyzed and clinically correlated. Bone age more than 2 years below the chronological age was taken as delayed age.

Deaths : After the completion of the study 5 patients died: 3 from Group II and I each from Groups I and III.

Statistical analysis was done using SPSS 10.0 for Windows. Frequencies for hemoglobin and serum ferritin were calculated. Paired t test and one-way analysis of variance were used for further analysis of data.

3 III. Results

Hemoglobin, Serum Ferritin and Other Conditions: Patients in all the three groups had low hemoglobin and high serum ferritin level. Only 6 patients had hemoglobin more than 9 but less than 10.0 mg/dL and another 6 had serum ferritin ? 2500 ng/L. Analysis of variance showed that there were significant differences (P>.001) between the hemoglobin and serum ferritin levels of the three groups. There was significant difference in these two parameters when group I was compared with group III (paired t test P>0.001) and when group II was compared with group III (paired t test P>0.001). There was no significant difference between the hemoglobin and serum ferritin levels of group I and II. Decline in serum ferritin was observed within first ;year of starting chelation therapy. Compliance to chelation therapy was generally good. Only two girls attained sexual maturity (one each from group II and III).

During study 2 patients were diagnosed to be suffering from hypothyroidism, 4 from cortisol deficiency, 2 from epilepsy and another 2 from congestive heart failure. None of the patients were HIV positive. Three patients had undergone splenectomy and 11 were sufferening from hypersplenism.

4 Radiological Findings

Bone age, bone density and bone expansion :

Radiographs showed that the boned age of 4 patients (1 patient from Group II and 3 patients from group III) less than it. X-rays of 3 patients (4.9%) from Group I (n=1) and II (n=2) were normal. Rest (96%) of the patients had mild to moderate expansion and reduction in bone density. Three patients (4.9%) 2 from Group I and 1 from group II had severe expansion and reduction in bone density. Erylmeyer flasking was observed in 5 (8%) patients: in the knee joints of 4 patients and in all the three joints elbow, knee, and ankle of 1 patient.

5 V. Peri-Articular Changes

Group I (Deferiprone) : Radiographs of 19 (43%) patients showed peri-articular changes in the knee joint which were clinically correlated with complaints of joint pain, stiffness, (consequently of limping), swelling, inability to squat and climb stirs (Table **??**). Out of these 19 patients, 7 patients had involvement of both the knees. Due to severe arthritis in the knee joints 2 patients were unable to walk and hence confined to bed. Peri-articular changes were present in the wrist joint of 9 (21%) patients, elbow joint of another 9 (21%) and in the ankle of 4 patients (10%). X-ray of 1 patient showed reduced space in elbow joint which clinically correlated with the patient's inability to flex arms. Soft tissue swelling was observed in one radiograph of the knee.

In 6 patients (14%), more than one join was affected. Arthritic changes were present in all the four joints of 2 patients, three joints (wrist, elbow and knee) of 1 patient, two joints (wrist and elbow) of 3 patients and wrist and knee of another 1 patient. Deferiprone of one patient was stopped due to severe arthralgia and swelling in knee joint (no chelation presently) and of another due to thrombocytopenia.

Knee joint was the most commonly affected joint and the most frequent symptom was pain and swelling in the joint. These symptoms appeared within first two years of starting deferiprone therapy.

Group II (Deferoxamine) and Group IIII (No Chelation):

Radiographs of patients in this group did not show any periarticular changes. None of the patients complained of joint pains or showed changes in total blood counts.

6 VI. Discussion

One of the major concerns with clinical use of L1 is the risk of associated toxicity 19 . Issues regarding safety of deferiprone have been discussed by the International Study Group for Oral Iron Chelators (ISGOIC), a group of about 40 scientists and clinical investigators with extensive experience in the management of thalassemia patients in 1993 in Nicosia 21 . Consensus was that there is an urgent need for further well controlled clinical studies of deferiprone in sufficient number of patients in order to enable proper judgment of its suitability for general long -term clinical use. The relative effectiveness and safety of and compliance with deferiprone and deferoxamine were compared in a prospective randomized trial begun in Canada in 1993.

The most common adverse effect associated with administration of deferiprone has been arthralgias, primarily, of the large joints the etiology of which remains elusive. The most serious adverse effect associated with the administration of deferiprone was severe neutropenia or agranulocytosis, first reported in 1980 20 . Till 1997 this complication had been reported in 13 patients, of whom 10 were thalassemia major patients 20,22,23 , as early as 6 weeks and up to 21 months after initiation of deferiprone. In five patients in whom rechallenge with deferiprone was attempted after white blood cell counts returned to normal, a second decrease in neutrophil count was observed 23 . The mechanism of deferiprone-induced neutropenia is unknown. Although studies in animals and early reports in humans suggested that this effect might be related to administration of high doses of deferiprone, at least 7 patients have developed agranulocytosis during administration of the standard daily dose of 75 mg/kg body weight; this adverse effect appears not to be dosedependent, but idiosyncratic and unpredictable.

Results of a long term-term deferiprone therapy show that 1 per 100 patients developed agranulocytosis, which was reversible. Other significant complications in decreasing order of incidence were: transient liver enzyme abnormalities (44%), arthropathy (21%) , zinc deficiency (14%) and nausea 80%)24. Joint symptoms in association with deferiprone therapy are known25. Joint symptoms occurred in up to 33% of patient in Indian trial15. In another study26, arthropathy caused discontinuation of deferiprone during second or third years of therapy. Joint symptoms were present for several weeks and did not improve with lowering the dose of deferiprone (to 50 mg/kg/d). The knee joints were mainly affected and the clinical symptoms were stiffness, crepitus, and effusion. However, despite conducting several tests pathophysiology of arthropathy could not be known 26 . Some degree of joint or muscle stiffness and pain affecting shoulder, back ankle, knee joint and osteoarthritis of the knees was reported in patients on deferiprone 25 . The explanation for joint symptoms was unclear.

Osteoarthropathy is well recognized in thalassemia major, usually in the second or third decade and is attributed to underlying bone changes 27 and lower limb pains are particularly frequent in thalassemia **??**8 . Other adverse effects reported with deferiprone administration include dermatologic changes associated with decreases in serum zinc concentration which resolve with oral zinc supplementation 29 , 30 , nausea, and transient or sustained liver enzyme abnormalities 24 .

Author has also

In the present study, although chelation therapy had brought down serum ferritin levels but they were still very high 31 . Only 6 patients were well chelated as they had serum ferritin ? 2500ng/dL. Results of this study

show expected bone changes (reduced bone density and bone expansion) in almost all the patients which can be attributed to persistently low hemoglobin levels. Involvement of knee joint (peri-articular) which supports the findings of previous studies 25,26 was the main finding of the study although these changes were observed in patients from group I only, that is, those patients who were on deferiprone and they were be clinically correlated (complains of pain, stiffness, swelling etc.). Knee joint involvement in this study is the highest reported so far 15,24 . Three patients suffered from join problems the most. In the first two cases, arthritic changes in the knee joints of two patients were so severe that they were unable to walk and were disabled. One of these patients died due to multiple organ involvement. In the third case, due to reduced joint space in the elbows the patients was unable to flex the arms. In a lesser degree of disablement, three more patients who had changes suggestive of arthritis in the knees, were unable to squat due to pain in the knees. Other serious adverse effect of deferiprone were repeated thrombocytopenia in 2 patients, leucopenia in 2 patients and bone marrow suppression in one. The patient developed hypersplenism, followed by thrombocytopenia (while still on deferiprone therapy) and finally bone marrow suppression. This patient switched over to deferoxamine therapy approximate 11 months prior to his death. However, after the study was completed, 7 patients switched over from deferiprone to deferoxamine therapy firstly due to join pains (3 males) and secondly in order to avoid any other associated complications (3 males and 1 female).

Deferiprone has a much lower therapeutic ratio than deferoxamine, for two reasons. First, deferiprone is considerably more toxic and regularly depresses the granulocyte count in both normal and iron-overloaded animals 32 , deferoxamine in contrast does not depress the marrow. In clinical studies deferiprone has caused both agranulocytosis and arthralgia or arthritis **??**3 . Second, Oliveri and her collegues clearly demonstrated that deferiprone can reduce iron stores to lower, if still elevated, levels in patients with severe iron overload, the drug has a concentration-dependent affinity for iron **??**4 . Three molecules of deferiprone are required to bind one molecule of iron, whereas deferoxamine binds iron tightly in a 1:1 ratio. For this reason, deferprone must be present at very high concentrations (close to toxic levels) to be effective. It dissociates from iron when the concentration of iron in body fluids falls to the level achieved just few hours after oral adminstration **??**4 . Hence as demonstrated by Olivieri and her colleagues, deferiprone does not readily reduce excessive body iron stores below a certain level. It is, therefore, not clear if the drug will provide long term protection from disease. Deferiprone is now well known to cause adverse effects on musculo-skeleton 4 ., though in some studies the symptoms have resolved on discontinuation of the drug.

Our study emphasizes the fact that patients who were on deferoxamine and those who were not on iron chelation did not suffer from arthritic problems. Since a lost of studies have reported similar musculoskeletal pains and osteoarthritis in patients on deferiprone therapy, it suggests that these symptoms are related to deferiprone therapy. An immunological mechanism could be responsible for these symptoms 25 . It is also possible that soluble LI-iron complexes of metabolites formed in the joints or transported there from plasma or LI itself may be implicated 25 . It is important that for future clinical studies, patients with preexisting clinical complications are included so that possible adverse effects of the drug can be easily distinguished from the progression of the underlying disease 25 .

The results of our study show that long-term iron chelation therapy is feasible using deferiprone but it is associated with serious side effects. Our study confirms the findings of previous studies in which different side effects of deferiprone have been reported 13,15,29. Keeping in mind financial constraints of low and middle socio-economic Indian families deferoxamine therapy has two main limitations: firstly, it is an expensive drug (both oral as well as infusion) not easily affordable by Indian families and secondly it calls for 10-12 hours of continuous subcutaneous infusion causing discomfort to the patient **??**5, **??**6 and hence poor compliance. On an average the annual expenditure of a patient on deferoxamine is Rs.1,00,000/-and that of a patient on deferiprone is Rs.12,000/-. From this is evident that deferiprone is relatively inexpensive compared to deferoxamine and hence, deferiprone is the only option for thalassemia major patient from low and middle socio-economic strata (since there is no national health policy supported by Indian Government) since this drug decreases the iron overload to a measurable extent. However, toxicity of deferiprone mandates a careful evaluation of the balance between risk and benefit to the patients with thalassemia who require life long iron chelation bringing into question its long term use in humans.

7 VII. Acknowledgement

[1] [2] [3]

Figure 1: ?

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page 121.

Clinical Details Sample Mean	Group I (42) Boys 29 9.57 -7.6 ±.88 5.4 9.0		Girls
Age (years) Delayed bone age			13
Hemoglobin X ±SD Minimum			8.69
Maximum			-
			8.1
			±.95
			6.3
			9.7
Serum Ferritin X ±SD Minimum	5322.5		3744.5
Maximum	±2657.7		±1838.2
	2,000		1326.
	10,073		6803.00
HIV	-		-
HCV Positive	5		1
Hypersplenism	11		
Splenectomy	-		2
Thrombocytopenia	2		-

Figure 2: Table : 1

Changes

				ear 2012 Y 7
Bone Density Norm -1 -2	Bone Expansion -3 Norm +1 +2	PARTICULR CHANGES Arthritic Changes +3 Norm Present	Reduced Joint Space Norm Present	STS Medical Research Volume XII Issue IX Version I Global Journal of

[Note: © 2012 Global Journals Inc. (US)]

Figure 3: Table Changes In

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