Journal of Cardiovascular Disease Research

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 06, 2024

A study of combined desferrioxamine and deferiprone versus single desferrioxamine therapy in patients with major thalassemia in a tertiary hospital in central india

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Abstract:

Background:

Thalassemia is a common disease in these parts of central India. The aim of this study was to investigate the efficacy and safety of oral iron chelators, deferiprone in combination with desferrioxamine in comparison with desferrioxamine alone.

Methodology:

A total of 70 transfusion-dependent thalassemia major patients were randomly selected to receive one of the following two treatments: deferiprone in combination with desferrioxamine (n=35, desferrioxamine+deferiprone group) or desferrioxamine alone (n=35, desferrioxamine-only group).

Results:

Serum ferritin decreased more significantly in patients on desferrioxamine+deferiprone therapy compared to patients who only received desferrioxamine Side effects of deferiprone, including neutropenia, severe gastrointestinal upset, and arthropathy occurred in eight, four, and two patients, respectively but none led to discontinuation of the treatment. Beta-thalassemia major patients with iron overload due to transfusion could be successfully treated with a combination of desferrioxamine and deferiprone. This regimen is more effective than

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 06, 2024

desferrioxamine-only therapy in decreasing serum ferritin; therefore, it also could be more effective in reducing iron overload and related complications in beta-thalessemia major patients.

Keywords: Thalassemia, iron chelation.

Introduction:

Thalassemia is a common disease in parts of central India with patients requiring frequent blood transfusions and hence iron overload. The availability of oral iron chelating with deferiprone (DFP) since 1987 has been useful but showed poor efficacy when used alone as compared with DFO. DFP, an oral iron chelator, has also been accepted in the list of approved drugs for thalassaemic patients and is used for patients in special cases such as inability to use DFO (due to incompliance or severe side effects) or an unsatisfactory response.2 It is prescribed at an average dose of 75 mg/kg/day. Combined iron chelation therapy with DFO and DFP is used in patients with severe ironrelated organ failure such as cardiomyopathy. Ironinduced cardiomyopathy is still the main cause of deaths in these patients.3

Materials and methods:

This study took place in the Department of Paediatrics in a tertiary hospital in Central India. It was a single-blind randomized clinical trial, was aimed to investigate the efficacy of combined DFO+DFP therapy compared with DFO-only therapy in β-thalassemia major patients. A total of 70 thalassemia major patients were selected randomly for this study. The patients were divided into two groups. Group1 consisted of 35 patients (16 males and19 females, the mean age: 18.4±3.85 years) who

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 06, 2024

received DFP (Deferiprone), 75 mg/kg/day in three divided doses in combination with DFO (Desferal, Novartis), 40- 50 mg/kg/day, three to five nights/week. Group 2 included 35 patients (15 males and 20 females, the mean age: 17.51 ± 4.78 years) who only received DFO which was selected from patients highly compliant to DFO treatment. All patients received packed red cells at intervals of three to four weeks to maintain a hemoglobin level above 9 g/dL. They had been treated with DFO prior to the commencement of the study. Iron-overloaded thalassemic patients, at least ten years old with a ferritin level greater than 2000 µg/L, were eligible for inclusion in the study. Based on the serum ferritin level, the patients were divided into three distinct groups for treatment. In addition to DFP, patients with serum ferritin levels between 2000 – 3000 µg/L received DFO three times a week, those with the level between 3000- 5000 µg/L received DFO four times a week, and the third group with the level above 5000 µg/L received DFO five times a week.

Thirty-five of these subjects were allocated to prospectively receive additional therapy with DFP, while 35 subjects only received DFO. Exclusion criteria were lack of compliance, known toxicity or intolerance preventing therapy with DFO and DFP, neutropenia, thrombocytopenia, renal or hepatic diseases, active viral illnessbeing treated with α-interferon/ribavirin, being HIV-positive, and pregnancy or nursing. Baseline investigations were completed within four weeks prior to the study. To evaluate the side effects, the patients gave a detailed clinical history and were examined at each visit. Changes in the serum ferritin level were considered as the primary efficacy end-point. Complete blood counts and differentials were assessed every seven to ten days for the first eight weeks and every two weeks thereafter. Serum ferritin concentrations, liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), blood urea nitrogen (BUN), and creatinine were

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 06, 2024

measured at intervals of six months. Liver iron concentration measurement, although desirable, could only be performed on a few patients enrolled in this study; hence, no correlation could be assessed. Statistical analyses were performed using SPSS.

Results:

Of the 35 patients taking DFP in the study, eight (22.9%) had neutropenia [absolute neutrophil count (ANC) below 1.5 ×109 /L], four (11.4%) developed severe gastrointestinal (GI) upset, three (8.6%) had persistently elevated liver enzymes, and two (5.7%) developed arthropathy. The dose of DFP was reduced to 50 mg/kg/day and the patients responded to the reduced dose. The side effects subsided so that the patients could continue participating in the study. None of these side effects were seen in patients on DFO-only therapy. Efficacy of treatment was determined by comparing changes of biochemical data within and between two groups of patients with different regimen therapies using repeated measures test. The results are shown in Table 1. Biochemical data included serum ferritin, BUN, creatinine, ALT, and AST which were measured before the treatment, and six and 12 months after the treatment in both groups.

The within subject test showed that serum ferritin, ALT, and AST had significant changes in each group, implying that these three parameters decreased significantly in each group after six and 12 months ($P<0.001$) The between groups test showed that the effect of variable group was statistically significant only regarding serum ferritin ($P<0.017$). It was not significant regarding other variables including BUN, creatinin, ALT, and AST. In other words, only serum ferritin showed a more

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 06, 2024

significant decrease in patients on DFO+DFP therapy in comparison to the patients on DFO-only therapy (Table 1).

Discussion:

It was first reported in 1998 that the simultaneous use of DFO and DFP had a commutative effect on daily urinary iron excretion.4 The combination regimen was superior and more efficient in achieving a negative iron balance than DFP. The net iron balance was significantly better in patients on combination therapy than on DFO monotherapy. The results of this study may confirm that beta-thalassemia major patients with iron overload due to transfusion respond better to a combination of DFO and DFP. This group of patients, who were considered nonresponsive/noncompliant to DFO therapy alone, was reported to be remarkably well with combination therapy. Our results are also in agreement with several recently reported studies.4–6 Wonke et al. in their study on combined therapy had to increase the daily dose of DFP in nine patients from 75 mg/kg to 83 – 100 mg/kg which resulted in a fall in serum ferritin level in them.4 Another study by Mourad et al. on 11 patients reported that the mean serum ferritin level decreased from 4153±517µg/L to 2805±327 µg/L on combined therapy.7 The effectiveness of the sequential use of DFP and DFO in children with thalassemia major from Turkey was reported by Aydinok et al.6 In this study, we evaluated the efficacy of combination therapy by serial assessment of serum ferritin levels at intervals of three months. The serum ferritin level fell from 4053±1452 µg/L to 3141±1429 µg/L after six months and to 2686±929 µg/L after 12 months that was statistically significant in comparison to patients who only received DFO. We can conclude that all the above-mentioned studies carried out in different parts of the world and our study favor the better

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 06, 2024

efficacy of combination therapy of DFO and DFP in reducing the burden of transfusion iron overload. Clinical experience has shown that the most serious side effect of DFP is agranulocytosis, which occurs in approximately 0.5% of patients and is more frequent in the first month of therapy as well as in patients with an intact spleen.8,9 In our study, eight patients developed neutropenia. Other complications that were recognized in patients on DFP treatment were as follows: GI upset in four and arthropathy in two patients. All of these side effects were tolerated well and none of them led to discontinuation of the treatment.

The study revealed that beta-thalassemia major patients with iron overload due to transfusion could be successfully treated with the combination of DFO and DFP. This regimen is more effective than DFO-only therapy in decreasing serum ferritin; therefore, it could be also more effective in reducing iron overload and related complications in beta-thalessemia major patients.

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ISSN: 0975-3583,0976-2833 VOL15, ISSUE 06, 2024

Tables:

Table 1: Comparison of biochemical data between two groups of patients on DFO-only therapy and combined DFO+DFP therapy.

		Serum ferritin Mean ± SD	BUN Mean ± SD	Creatinine Mean ± SD	ALT Mean ± SD	AST Mean ± SD
DFO group N=35	Before treatment After 6 months After 12 months	4272±1563 4154±1758 4107±1411	11.8±3.1 11.54±3.39 11.74±2.8	0.474±0.16 0.437±0.13 0.409±0.11	40.4±24.3 36.17±21.8 35±20.9	38.17±20.16 36.54±18.57 31.89±15.03
DFO + DFP group N=35	Before treatment After 6 months After 12 months	4053±1452 3141±1429 2686±929	13.63±4.08 12.09±2.87 121.74±2.21	0.454±0.11 0.454±0.08 0.451±0.12	45.03±47.7 39.6±37.6 39.03±60.4	38.09±19.6 38.09±33.5 28.63±18.4
P value (between subject effects)		<0.017 <0.000	NS NS	NS NS	NS <0.0001	NS <0.0001

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 06, 2024

(within subject effects)						

DFO=Desferrioxamine, DFP=Deferiprone