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Research Article

A Comparison of Ferritin Serum Levels of Patients Diagnosed with ThalassemiaTreated with Oral and/or Injection Blood Iron Chelators in Jahrom, Iran (2011-2012)

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ABSTRACT

Introduction: Hemochromatosis especially in the heart is the leading mortality cause of thalassemia major patients. Chelation therapy is an important treatment in this regard. The goal of this article is to compare three methods in reducing the ferritin serum levels of patients diagnosed with thalassemia in Cooley Center of Jahrom, Iran. These methods are oral treatment (Deferiproneor Osveral), injection (Desferal), and combined (oral and injection).

Methodology: This is a clinical trial. Thalassemia major patients were assigned into two groups based on their ferritin levels: <6000 and ≥6000. The patients with ferritin<6000 randomly underwent oral, injection, and combined treatments. Those with ferritin≥6000 underwent the combined treatment. Patients were physically examined every three months. Serum ferritin, average hemoglobin, BUN, CR, ALT, and AST were measured. Descriptive statistical methods (mean, percentage, and standard deviation) were used. Then, the data were compared by ANOVA in SPSS 11.

Results: 72 thalassemia major patients visiting the Cooley Center of Motaharti Hospital of Jahrom, Iran participated in this study. In this study, 39 patients were female (54.2%) and 33 were male (45.8%). The patients were assigned into three groups and followed up for a year. Ferritin decreased by 275.26±170.55, 879.11±250.79, and 2078±474.92 Ng / ml in oral, injection, and combined groups at the end of the study, respectively. A significant difference was found in the combined group compared to the other two groups. However, no significant difference was found in terms of increased BUN, CR, ALT, and AST, decreased WBC, and type of medication.

Conclusion: The results show that the combined treatment is more effective in reducing ferritin level.

Keywords: Ferritin, Thalassemia, Desferal, Osveral, Deferiprone.

INTRODUCTION

Thalassemia major is a blood disorder of inherited hemoglobin synthesis which results in severe anemia. Since frequent blood transfusions is necessary for maintaining normal blood hemoglobin, increased iron level and then deposition in many tissues cause all problems of thalassemia patients. Iron deposits in the liver, heart, bone marrow, and endocrine glands including pancreas, parathyroid glands, and other tissues are responsible for many problems [1]. Most deaths are due to iron deposition in patients' hearts [2]. Therefore, reducing ferritin using iron chelators can significantly help the complications. Iron chelation therapy is the main treatment for the thalassemia major patients [3]. So far,iron chelation injection has been common; however, it is time-taking and painful. Such treatment must be applied during weekdays for several hours [4]. Lack of access to the drugs for most patients and the inability of

these drugs to treat complications in the rest of the patients have led to the discovery of other iron chelators [5]. New oral iron chelators are more tolerable for the patients, too [4]. However, these drugs are not effective for all patients because long-term intake contributes to the increased serum ferritin or liver iron in some patients and certain complications such as neutropenia, agranulocytosis, gastrointestinal disorders, increased liver enzymes, joint involvement and zinc deficiency in other patients [6]. However, studies have shown that oral iron chelators are more effective than the injection and reported fewer complications [7]. Extensive studies in the world and Iran have compared the effect of oral and injection separately and simultaneously. These studies have shown that the intake of each drug has been helpful; however, most of these studies have reported that the combined use of oral and injecteddrugs caused the greatest decreased serum ferritin level. Combined treatment has been advised for high ferritin cases [8]. Arthralgia and nausea are the only complications. On the other hand, it is tolerable by most patients because the frequency ofblood iron injection decreased from 5 times to twice a week [9]. Although several studies have been conducted on the oral and injected iron for thalassemia patients, few have reported the injection method a suitable treatment. Others believe that oral chelators are better choices. Some researchers have claimed that simultaneous consumption of oral and injectedchelators are the best treatment. This article aimed to find the best treatment method.

METHODOLOGY

This is a clinical trial in Cooley Center of Motahari Hospital of Jahrom, Iran. Total number of patients visiting the center was 120 of which 72 had thalassemia major. The remaining 48 were thalassemia intermedia and Sickle cell patients. They were excluded from the study because of the irregular visit to the center and the confounding factor prevention. Therefore, 72 patients were selected for the study. The patients with ferritin<6000 were randomly assigned into three groups:

Group I: They received oral blood iron chelators. The drugs used for these participants were DeferiproneandOsveral(L1). 20-30 Osveral and 50-75 L1 $^{mg}/_{kg}/_{day}$ were administered.

Group II: The patients received injected blood iron. 40-60$^{mg}/_{kg}/_{day}$ Desferal was prescribed.

Group III: The patients received the combined treatment (oral and injection): Desferal+ Deferiprone or Desferal+ Osveral.

The patients with ferritin ≥6000 only received the combined treatment.

Then ferritin serum level, liver enzymes, renal function, Hb, white blood cell count were measured within a year starting from January 2011 to January 2012. Mean ferritin reduction was then compared between the groups. The data were analyzed at descriptive level in SPSS 11. Then they were compared by ANOVA.

RESULTS

In this study, 72 thalassemia major patients visiting the Cooley Center of Motaharti Hospital of Jahrom, Iran participated. 39 patients were female (54.2%) and 33 were male (45.8%). The patients' age ranged between 6 and 42. The mean age was 24. The subjects were randomly assigned into three groups in terms of iron chelators:

In Group I, the 30 participants (41.7%) only received oral iron drug. 15 patients (20.8%) were male and 15 (20.8%) were female. The second group (injection) consisted of 17 (23.6%) patients. In this group, 8 patients (11.1%) were male and 9 were female (12.5%). The combined group consisted of 25 patients (34.7%). In this group, 10 (13.9%) were male and 15 (20.8%) were female.

Table 1: Type of Iron Chelation used by Thalassemia Major Patients of Jahrom, Iran-2011-2012

Type of Medication	Male		Female		Total Thalassemia Patients	
	Number	%	Number	%	Number	%
Oral	15	20.8	15	20.8	30	41.7
Injection	8	11.1	9	12.5	17	23.6
Combined	10	13.9	15	20.8	25	34.7
Total	33	45.8	39	54.2	72	100

At the beginning of the study, patients were assigned into two groups based on serum ferritin levels:

- ✓ Ferritin<6000
- ✓ Ferritin≥6000

The patients with ferritin<6000 were randomly assigned into three groups in terms of iron chelation.

- ✓ Oral drugs: Two types of oral drugs were used: Deferasirox (Osveral) with the daily dose of 20-30 mg⁄(kg⁄day) based on iron overload and Deferiprone (L_1) with daily dose of 50-75 mg/(kg/day)
- ✓ Injection drugs: The second group received only injection drugs. Deferoxamine (Desferal) is given at a dose of 60-40 mg / kg and was subcutaneously administered over a period of 8 to 12 hours a day.
- ✓ The third group received combined treatment (Oral + Injection): Desferal+ Deferiprone or Desferal+ Osveral.

The patients with ferritin ≥6000 only received the combined treatment. We measured the ferritin at the beginning of the study and then at intervals of 3 months for a year. After a year, the ferritin reduction was compared with that of the beginning. The patients who received combined treatment exhibited greater ferritin serum level reduction than those only received either oral or injection treatment. The difference was statistically different (P=0.001). However, no significant difference was found between the first (oral) and second (injection) groups in terms of ferritin serum level reduction (P=0.219).

Table 2: Mean ferritin serum level reduction at Start and End of each treatment and reduction

Mean ferritin serum level	Start	End	Reduction
Oral	2129.86±1624.18	1754.6±1641.56	275.26±170.55
Injection	3991.94±2332.43	3112.82±2319.76	879.11±250.79
Combined	4901.36±3039.25	2814.2±2262.21	2087.16±474.92

Liver enzymes (ALP, ALT, and AST) were periodically measured at intervals of 3 months. The patients were under control in terms of normal or increased liver enzymes in this period. At the end of the year, no significant relationship was found between the types of medication and increased liver enzyme level.

Type of medication and AST: P=0.19

Type of medication and ALT: P=0.41

Type of medication and ALP: P=0.41

The patients were also evaluated in terms of renal performance (BUN and Cr) every three months. Increased BUN and Cr was measured. Out of 72 patients, only one patient experienced increased BUN and one experienced increased Cr. However, the increase was not big enough to require drug discontinuation. On the other hand, type of medications had no significant relationship with increased BUN and Cr (BUN P=0.35, Cr P=0.41). The patients were evaluated in terms of Hb and increased or decreased WBC (leukopenia or leukocytosis). Out of 72 patients, only 25 experienced decreased Hb (Hb<10). Type of medication had no significant relationship with decreased Hb (P=0.21). WBC level was also measured. One out of 72 patients developed leukopenia. Drug discontinuation was not required in this case. 23 out of 72 patients developed leukocytosis (WBC>12000). Type of medication had no significant relationship with increased or decreased WBS (P=0.36).

Table 3: WBC and Drug Consumption

Type of Medication	Normal		Increase		Decrease	
	Number	%	Number	%	Number	%
Oral	20	27.8	10	13.9	0	0
Injection	12	16.7	5	6.9	0	0
Combined	16	22.2	8	11.1	1	1.4
Total	48	66.7	23	3.9	1	1.4

Table 4: Hb andDrug Consumption

Type of Medication	Normal		Decrease	
	Number	%	Number	%
Oral	18	25	12	6.7
Injection	11	15.3	6	8.3
Combined	18	25	7	9.7
Total	47	65.3	25	34.7

DISCUSSION

In 1960 before the repeated blood transfusions and advances in the iron chelation therapy, thalassemia patients had severe and irreversible complications. These complications mostly affect patients in the second decade of life and were responsible for the death. In 2000, the average age of patients rose to 35 following the extensive advances in iron removal so that a study in California University showed that 50% of the patients had reached over the age of 35 and 83% over 20 years old [10]. Given the fact that various drugs and different methods are used today to reduce the level of extra iron in patients diagnosed with thalassemia major, especially those with severe iron overload, it is essential to reduce the ferritin serum levels to deal with the iron deposition complications in organs like the heart, kidneys and liver, and improve the patients' quality of life. According to different studies in Iran and worldwide to find the best treatment method, we also tried to compare three types of treatment (oral, injection, and combined) to find out which method is capable of reducing ferritin serum levels and evaluate the complications. Therefore, Cooley Center of Motahri Hospital of Jahrom, Iran was selected and the patients were evaluated for one year. Out of total number of 120 patients visiting the center, 72 suffered from the thalassemia major (39 female (54.2%) and 33 male (45.8%)). The patients' age ranged between 6 and 42. The mean age was 24 years. They were randomly assigned into three groups: oral, 30 patients (41.7%); injection, 17 patients (23.6%); and combined, 25 patients (34.7%). The mean ferritin serum reduction was 275.26±170.55 in oral group. It was 879.11±250.79 and 2087.16±474.92 in injection and combined groups, respectively. No significant difference was found between the combined method and the other two groups (P=0.001). In this study, combined therapy was more effective in reducing the ferritin of the patients diagnosed with thalassemia major. The studies conducted in other regions are also consistent with ours. The study by Dar et al. in Oman showed that a six-month period of combined treatment significantly reduced the ferritin compared to the Deferoxamine treatment [11]. The study by Oriagi et al. in Italy on combined treatment of 50 out of 55 patients diagnosed with thalassemia major showed that ferritin decreased significantly [12].The study by Draconci et al. (2010) on 21 thalassemia major patients showed that the combined treatment was better in reducing iron blood level [13]. The study by Peng et al. on 114 β-thalassemia major patients in Taiwan reported thatDeferoxamine therapy, Deferiprone therapy, and combined treatment (Deferoxamine and Deferiprone) significantly reduced the ferritin [14]. The study by Katamys et al. in Greece on 43 β-thalassemia patients undergoing Deferoxamine and Deferiprone therapy three days a week for a year showed that ferritin decreased significantly [15].The study by Zareiee far et al. in Shiraz, Iran showed that serum ferritin decreased significantly in patients undergoing the combined treatment compared to those undergoing Deferoxamine treatment [16]. Another study by Karami et al. in Mazandaran Province, Iran showed that the combined treatment was better in reducing the serum ferritin [17].The study by RashidiQader et al. in Mazandaran Province, Iran concluded that the combined treatment effectively reduced the serum ferritin [18].Recent studies have all shown that the combined treatment is better in reducing the serum ferritin, which are consistent with our study. The patients were examined in terms of complications such as increased liver enzymes, leukopenia, and increased BUN and Cr for a year. 9 patients (12.5%) experienced increased AST of which 3 patients (4.2%) were in oral group, 1 (1.4%) was in injection group, and 5 (6.9%) were in the combined group. In this study, 13 patients experienced increased ALT of which 6 patients (8.3%) were in oral group. 3 (4.2%) and 4 (5.6%) were in injection and combined groups. In this study, 25 patients (34.7%) experienced increased ALP of which 11 (15.3%) were oral group. 6 (8.3%) and 8 (11.1%) were in combined groups, respectively. However, the increase was not big enough to require drug discontinuation. In this study, the number of patients in oral and injection groups and experienced increased liver enzyme was more than those in the combined group. However, the difference was not statistically significant (P>0.05). This is consistent with the

study by Magio et al. (2002) in Italy because the subjects in oral group developed increased liver enzymes [19]. The study by Katamys et al. also showed that 18% of the participants in oral group experienced increased liver enzyme, which is consistent with our study [15]. The study by Hashemiyeh et al. in Arak Province, Iran on 33 thalassemia major patients undergoing Deferiprone pills showed that 60% (20 patients) developed increased AST and 35% (14 patients) experienced increased ALT [20]. The increase was greater compared to our study. In our study, 4.2% of the patients experienced increased AST in oral group and 8.3% experienced increased ALT in oral group. One patient developed leukopenia; however, none developed agranulocytosis and drug discontinuation was not required. The study by Katamys et al.in Greece showed that agranulocytosis was 4.2 cased per 100 a year, which is inconsistent with our study [15]. In the study by Jamvar et al., two patients developed agranulocytosis during the study. It did not occur in our study [21].In the study by Oriagi et al, 3 patients developed agranulocytosis and 7 developed leukopenia [12]. The study by Hashemiyeh et al.reported one leukopenia case (3%); however, no case of leukopenia was seen in oral group in our study [20]. The patients were evaluated in terms of increased BUN and Cr. One patient (1.4%) in combined group experienced increased BUN and one in oral group (1.4%) experienced increased Cr. Other studies have not focused on this topic.

CONCLUSION

According to this and other studies in Iran and the world, combined treatment (Desferal and oral iron chelator) is the best method for treating the iron overload caused by frequent blood transfusion for thalassemia major patients with high serum ferritin. The method results in decreased serum ferritin to less than 1500. When the serum ferritin reaches less than 1500, oral iron chelators can be used because several studies have shown than oral medications such as L_1 have similar effects like Desferal in reducing the serum ferritin. Since long-term Desferal injection leads to several problems, more attention has been given to oral medications. On the other hand, oral medications are very helpful in reducing low ferritin.

RECOMMENDATIONS

1. First, combined treatment is advised for the thalassemia major patients with high ferritin serum levels. Then, when the ferritin reaches between 1500 and 2000, either oral or injection method is advised.
2. Either oral or injection method can be used for the patients with ferritin serum less than 2000.

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