

Combined Desferrioxamine (Desferal) and Deferasirox in Children

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Abstract: Recurrent blood transfusion as a supportive treatment for major thalassemic patients would eventually produce an iron overload, severe consequences and even mortality. A number of iron chelators are used to reduce its side effects. The present research seeks to compare the level of serum ferritin in major thalassemic patients in the Desferal treatment group and the other group treated with Desferal and deferasirox together, in Bandar Abbas (2012-13). 94 major thalassemic patients dependent on blood transfusion were selected and then randomly divided in two groups. 48 participants belonged to the counter-Desferal (deferrioxamine) group with a dosage of 50 mg/kg transfused 3 times a week. 46 participants belonged to the group treated with Desferal combined with oral deferasirox (20-40 mg/kg) for the duration of one year. The level of ferritin was measured before the study and 3, 6, 9 and 12 months later. Alterations in liver enzymes, a complete blood test and the level of creatinine were measured before the research and also 12 months later. Having been collected, the data were analyzed using descriptive statistical tests and t-test. Results revealed that Ferritin level of the control group were $4094.4 \pm 4552.84 \mu\text{g/L}$ at the outset and was altered to $3441.2 \pm 1910.0 \mu\text{g/L}$ at the end. In the treatment group, it reduced from $4004.8 \pm 1717.14 \mu\text{g/L}$ to $529.04 \pm 1540.36 \mu\text{g/L}$. The degree of reduction was not statistically significant. A slight amount of leukocytosis and an increase in liver enzymes were observed, but not to a significant degree. the combinational treatment of deferasirox and deferrioxamine lowered the serum level of ferritin. However, it was not more effective than treatment with the mere deferrioxamine. We suggest more controlled research to be conducted to better investigate the medical effect and consequences of the combinational treatment compared to the single treatment.

Key words: Deferasirox • Deferrioxamine • Iron Overload • Thalassemia

INTRODUCTION

Thalassemia is a genetic disorder caused by alpha globin or beta globin gene mutation resulting in an ineffective synthesis in hemoglobin chain [1]. Thalassemia and in general hemoglobinopathies are the most prevalent non-genetic disorders in human beings and are considered as major threats to public health in some parts of the world [2,3]. Patients with chronic anemia such as thalassemia, cyclic diseases require regular blood transfusion to improve the quality of their life and to survive. Human beings are not capable of naturally excreting iron overload. They just store it in the form of hemosiderin and ferritin in liver, spleen and other endocrine organs [4]. Accumulation of iron toxins causes tissue damage and also heart failure, diabetes,

hyperthyroidism, lung failure and various side effects. The rate of mortality induced by recurrent transfusion among thalassemic patients due to the effects of iron is usually higher than the background disease among which heart failure is the most fatal (accounting for 50% of mortalities) [5]. Treatment with chelators is used to reduce these consequences. It helps to lengthen one's life for a considerable 3 to 5 times as long [6,7]. In Europe, three iron chelators are used: Deferrioxamine (transfused), the two oral chelators, Deferiprone and Deferasirox (Desferal). Deferrioxamine is known as the first biological chelator affecting iron and has improved the life quality of patients with high iron overloads to a considerable degree. Orally, it is not effective since it is very soon excreted through the urine. Deferasirox, used in other chronic anemia including major thalassemia, has been shown in a

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great body of research to considerably lower iron overload [8]. Various researches have been conducted to investigate the efficacy of different chelators in lowering iron overload. Its effect, whether alone or in combination, has been explored in different studies. Divergent findings have been obtained [9-11]. Considering the prevalence of major thalassemia in Bandar Abbas and the crucial role of iron overload accompanied by its consequences among children; we decided to conduct the present research. It is intended to measure the serum ferritin in major thalassemic patients in the control group under the mere effect of Desferal and the treatment group under the combinational effect of Desferal and deferasirox in Bandar Abbas in 2012-13.

MATERIALS AND METHODS

This study was a randomized clinical trial conducted in the thalassemia medical center of Bandar Abbas in 2012-13. Having obtained the written and informed consent of their parents, 100 major thalassemic children between 2 to 15 years of age were selected who had high levels of serum ferritin (>2000 ng/ml) despite the treatment with Desferal (the dosage of 50 mg/kg transfused three times a week). Randomly and in the order of visiting the center, they were divided in two 50-member groups. One group had been previously treated with Desferal and the other group (the experimental group) was treated for one year with a combination of Desferal and oral Deferasirox (20-40 mg/kg). In case there was no desirable response, the dosage was altered to 20 mg/kg and when no consequences were observed, it was increased to 40 mg/kg. Before the study began, a series of tests including diff, CBC and LFT were given to the participants who were repeated at the end for both groups. Exclusion criteria were: occurrence of any intolerable side effects in kidney, liver, etc. and consumption of drugs intervening with the target ones. The level of serum ferritin was measured every three months up to a year via the Italian liason instrument. Having been collected, the data were analyzed by SPSS ver. 16 and using descriptive statistics (frequency, mean, SD) as well as t-test. The significance level was set at <.05.

RESULTS

Finally, 94 participants entered this study. 48 members (51.1%) belonged to group A and 46 people belonged to group B (49.9%). Those who were excluded had not met the inclusion criteria. 44 of the participants (46.8%) were male while 48 of them were female (53.2%). Their mean age was 12.23±4.09 years. In group A it was 11.79±3.86 and in the other group it was 12.69±4.30 years. Average 11.06±4.17 µg/L years had passed from the diagnosis of their diseases. This time span for the members of group A was 10.53±4.03 and for the other group was 11.60±4.28 years. In the meanwhile, the participants received an average 1.32 units of blood transfusion. This amount of blood was transfused within an average 18.13±5.06 days. In the first group, average 1.41±.59 units of blood were transfused within 17.40±4 days. In the second group, 1.23±.42 units were transfused within 18.88±5.92 days. The mean initial ferritin level of participants was 4050.6±3450.27 µg/L. In group A, this level was 4094.4±4552.84 µg/L while in group B, it was 4004.8±1717.14 µg/LAs it can be seen in Table 1, no significant divergence existed between the ferritin level of these patients in the 1st, 2nd, 3rd and 4th three months.

Table 2 is indicative of neutrophil, ALT, AST, ALP and Hb level once at the outset and once again at the end of the study in the two groups. No significant difference can be observed between these values at the beginning and end of the study.

DISCUSSION

Patients afflicted with major thalassemia, due to ineffective hematopoiesis, have a higher absorption of iron in their metabolic system. Moreover, they require regular blood transfusion [12]. Among the serious consequences of major thalassemia is the accumulation of iron in body which makes keeping the balance of iron essential for survival [13]. Through a timely and adequate treatment with chelators, a great many of these patients retain their natural growth [14].

Table 1: Ferritin level in the 1st, 2nd, 3rd and 4th three months

Ferritin level (µg/L)	group A	group B	Total	p-value
Primary	4094.4±4552.84	4004.8±1717.14	4050.6±3450.27	-----
1st three months	3953.5±2365.39	4595.2±2121.78	4267.6±2260.52	0.169
2ndthree months	4425.8±2045.77	4073.9±2060.44	3583.3±1833.75	0.105
3rdthree months	3583.3±1833.75	3826.9±2092.2	3702.5±1957.66	0.551
4ththree months	3441.2±1910.0	3529.04±1540.36	3483.7±1732.20	0.807

Table 2: Neutrophil, ALT, AST, ALP and Hb level

	group A	group B	Total	p-value
1st neutrophil (µg/L)	±7.91 54.49	56.23±8	55.34 ±7.96	0.291
finally neutrophil(µg/L)	±8.94 55.96	54.65±8.94	55.32 ±8.65	----
(g/dL)1st ALT	±29.84 58.25	70.21±46.32	64.10±39.04	
finally ALT (g/dL)	±20.01 54.58	61.60±29.75	58.02 ±25.36	0.185
(g/dL) 1st AST	±25.99 56.45	66.76±36.17	61.50 ±31.64	
finally AST (g/dL)	±18.63 51.81	59.19±21.02	55.42 ±20.07	0.075
(g/dL) 1st ALP	±155.38 377.22	427.8±162.28	401.7 ±159.92	
finally ALP (g/dL)	±117.73 334	431.78±135.98	383.98 ±135.87	<0.001
1st Hb (g/dL)	8.98 ± 1.18	9.11±1.27	9.05±1.22	
finally Hb (g/dL)	9.46 ± 0.77	9.10 ± 0.91	9.29 ± 0.86	0.04

Desferal is one of the natural siderophore carrier of iron [15] and Deferasirox is also an effective iron chelator. It can cause an increase in creatinine, liver enzymes, abdominal pain and metabolic symptoms. Among children, however, it has had no impeding effect on their growth [16, 17]. Our aim, in the present study, was to measure the serum ferritin level among major thalassemic patients in the treatment group under the mere effect of Desferal and in the control group under the combinational effect of Desferal and deferasirox.

As the results revealed, although the ferritin level was lowered after the treatment, this divergence was not statistically significant. However, the two treatments were shown to be effective in lowering the level of ferritin. The previous body of research had either focused on the single effect of iron chelators or their combinational effect with medications other than those studied in ours.

In his research, Merchant concluded that a treatment with the single effect of Desferal (deferioxamine) lowers iron overload to a great extent [18]. Eshghi *et al.* [19] in a study conducted in a hospital in Tehran, emphasized that deferasirox even in its Iranian type (Osveral) is effective in lowering iron overload. Similar to Merchant *et al.* and other body of research, our study also revealed that treatment with the single effect of Desferal can significantly lower iron overload [18].

In two studies, Fisher *et al.* [20] and Tanner *et al.* [21] found the combinational effect of deferiprone and deferasirox to be stronger than the single effect of deferasirox. Kattamis *et al.* reported the positive combinational effect of deferiprone and deferioxamine (Desferal) in lowering the level of ferritin [22]. Based on their findings, Zareifar *et al.* found the combinational medical effectiveness of deferiprone and deferioxamine higher than the single effect of deferioxamine [23].

In our study, the combinational treatment with deferasirox and Desferal was not significantly different from the single treatment with Desferal. However, in Lal *et al.* [25], oskaridou *et al.* [26] (despite being a case

study) the combinational effect of the treatment was found to be moderate. This result could vary if they had used a larger sample. A single case could not be very reliable and indicative. In a research on animals, Otto-Duessel *et al.* [27] compared the combinational effect of these two drugs with deferasirox. They concluded that treatment with the mere deferasirox was more effective than the combined effect of deferasirox and Desferal. Their combination was found to be good but this does not improve the circumstances. No combinational effect was investigated in Keikhaei [24] and Balooch *et al.* [28].

Among the possible reasons for divergent results, mention can be made of different age groups. In the present study, the mean age was below 15 year. In the other studies [23-25], various age groups participated. Another factor could be the lower number of participants in the control group than the treatment group. There must be more or equal number of participants in the control group. However, the difference was not too much.

One limitation of this study was patients did not take their medication as they were told according to the research protocols. This could significantly affect the results. There are other limitations as well such as differences in the manufacturing companies of the medicines. Some patients took foreign medicines while the others took the Iranian ones. The efficacy divergence of these medicines could have affected the results. Among the merits of this research is the fact that it is one of the pioneering studies focused on the combinational effect of medicines. More research of this type is recommended to be conducted on more homogeneous sample of patients and with fewer limitations. Therefore, more significant results can be obtained.

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