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Comparison of Therapeutic Response and Complications of Oral Osveral and Injection Desfereal Chelating Agent in Patient with Thalassemia Major

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ABSTRACT: Iron overload is frequently leads to excessive iron deposition observed in patients with thalassemia because they receive frequent blood transfusion. Deferasirox, new oral iron chelators reduce iron load in transfusion-dependent patients. This study was performed to compare the efficacy and side effects of Desfereal versus Osveral in treatment of iron overload in transfusion patients with β-Thalassemia and intermediate thalassemia in Bandarabbas. Method: This clinical trial study performed on one hundred and thirty eight (above of two years) with β-Thalassemia and intermediate Thalassemia in Bandar Abbas. Patients were assigned randomly in two groups (69 cases in Osveral group and 69 cases in deferral group). Complete blood count, serum levels of Alanine aminotransferase (ALT), aspartate aminotransferase (AST), ferritin and creatinine were measured in both groups. First group receive 20 mg/kg oral Osveral daily and second group receive 40 mg/kg subcutaneous Desfereal per 12 hours. Complete blood count, serum levels of ALT, AST, ferritin and creatinine were measured in both groups. The cases reevaluated after 4 and 8 months. The date was analyzed by SPSS version 16 software using descriptive, Chi-square test and T-test. Significant level was set as P<0.005. Results: A total of 138 transfusion dependent patients received Osveral (n=69) or Desfereal (n=69). Decrease serum level of ferritin and hemoglobin there was significantly but this difference no significant in both groups. Abnormal laboratory studies with Osveral were associated with mild leukopenia (4.3%) and thrombocytopenia (5.8%) and with Desfereal were associated thrombocytopenia (1.4%). Conclusion: In this study transfusion dependent patient with thalassemia we observed a significant decrease in serum ferritin and hemoglobin with oral Osveral and Desfereal. Osveral is an oral iron chelator has acceptable tolerability and appears to have similar effects to Desfereal in decreasing serum iron in patients with iron overload. More randomized studies should be undertaken to determine the effects and side effects of iron chelators for treatment of iron overload.

Key words: Iron overload, Osveral, Desfereal, Thalassemia

ORIGINAL ARTICLE

INTRODUCTION

Iron accumulation is one of the most common disorders that occur in patients with repeated transfusion. Patients with β-thalassemia major require regular transfusion therapy to sustain life (Wonke, 2001). While such therapy effectively treats their anemia, the iron present in the hemoglobin of the transfused blood is retained in the body, since there is no physiological means of excreting it (Graziano et al., 1974). Iron accumulates primarily in the liver and spleen, and to a lesser extent in the heart, pancreas, and other organs (Hershko, 2010). This excess iron catalyzes the formation of reactive oxygen species (Halliwell et al., 1989), which damage a variety of macromolecule sand cell structures leading to hepatic cirrhosis, endocrine abnormalities (Perera et al., 2010), cardiac disease, and eventually premature death. The use of chelating agents has proven to be highly effective, being associated with reductions in both morbidity and mortality (¬Telfer et al., 2009) However, the available chelating agents have significant limitations. Transfused blood contains 200- 250 mg of iron per unit. Hence, patients with β-thalassemia major (TM) or other refractory anemia's receiving (Kwiatkowski, 2011) units of blood per month have an annual intake of 5000-10 000 mg of iron or 0.3-0.6 mg/kg/day. The body has no mechanism

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for excreting this excess iron. Moreover, patients with TM and other anemia characterized by ineffective erythropoiesis absorb excess iron despite iron overload because of production of GDF15 and possibly other proteins (eg, TWSGI) from erythroblasts, which inhibit hepcidin synthesis.

DFO:

DFO is the drug for which there is the longest experience in treating transfusion iron overload. Some units give intravenous DFO (from a separate bag) with blood transfusion (eg, 1 g of DFO for each unit of blood), but we do not recommend this in children or in adults unless noncompliant and inadequately chelated. The drug has transformed life expectancy for many patients with TM and other refractory anemia. It has also reduced endocrine and hepatic complications. Many patients with TM are not satisfactorily chelated by it, however, and then may develop a fatal cardiomyopathy. The reasons for these "failures" of DFO therapy include cost of the drug, pump and tubing, poor compliance (Telfer et al., 2000), allergy, toxicity, local problems at the site of the infusions, lack of 24-hour binding of NTBI (Porter et al., 1996), and Yersinia infection (not a complication of the oral chelators) . The main side effects occur with high doses of the drug in patients, particularly children, with low iron stores. These consist of damage to the retina (night blindness, visual field loss, retinal pigmentation, and changes on electrical tests) and high tone sensory neural hearing loss. Growth and bone defects may also occur in children, with rickets-like bone lesions, metaphyseal changes, and spinal damage with loss of sitting height. A therapeutic index can be calculated as follows: mean daily dose (mg/kg)/current serum ferritin (_g/L). If this is _ 0.025 at all times, these side effects of DFO do not occur (Porter et al., 1989). Regular checks are needed for visual or auditory defects, in children every 6 months and in adults annually. In children, checks of growth, particularly sitting height compared with total height, detect early spinal growth defects.

DFP (L1, 1, 2 dimethyl, 3 hydroxy, pyrid-4-one, Ferriprox):

This bidentate iron chelator is rapidly absorbed with a peak blood level about 45 minutes after ingestion. DFP has emerged as superior to DFO at reducing cardiac iron levels. DFP also seemed superior to DFX at lowering cardiac iron. The most side effects of deferiprone are gastrointestinal, such as nausea, vomiting, and abdominal pain. The most serious side effect of DFP is agranulocytosis, a neutrophil count of _ 0.5 _ 109/L in 2 consecutive blood tests. It occurs in 1% of patients, most frequently in the first year of treatment, but it has been described in the second year or rarely, later. It is reversible, but some deaths have occurred. The median duration of agranulocytosis is 9 days (range, 3-85 days). An arthropathy affecting mainly large joints, especially the knees, occurs in a proportion of patients. The arthropathy usually resolves after stopping the drug, and often the drug can be successfully reintroduced at the same or a lower dose. Patients may also develop pains in the muscles, which resolve without interrupting an arthropathy affecting mainly large joints, especially the knees, occurs in a proportion of patients. Transient rises in liver enzymes occur in 7% of patients, but these usually fall to normal without stopping the drug. In 1% of patients, the rises persist and the drug is then discontinued. The drug does not cause liver fibrosis (Hoffbrand et al., 2003). Zinc deficiency was first reported to occur in diabetic TM patients receiving DFP, and this was associated with increased urine zinc excretion (Cohen et al., 2003). In large trials, there has been a small overall fall in plasma zinc levels but few below the normal range. The deficiency is easily detected by measuring serum zinc levels and corrected with zinc supplements without diminishing iron chelation efficacy. Main side effects of DFX are Gastrointestinal, rash, renal and liver.

MATERIAL AND METHODS

This clinical trial study was performed on 138 patients with β-Thalassemia and intermediate Bandar Abbas Pediatric Hematology Clinic in September 2008 to March 2010. Inclusion criteria included the following: Patients with major thalassemia and intermediate thalassemia older than two years, serum ferittinin more than 1000, Normal creatinine, acceptable complete blood count (CBC), negative PCR in terms of HCV, negative HBV and HIV, Absence of heart disease and cardiac drugs, EF>55%, and absence of Proteinuria. Complete blood count test, kidney tests such as Cr and BUN, urinalysis for proteinuria review was performed on all patients. Patients were assigned randomly in two groups (69 cases in Osveral group and 69 cases in deferral group). Complete blood count, serum levels of Alanine aminotransferase (ALT), aspartate aminotransferase (AST), ferritin and creatinine were measured in both groups. First group receive 20 mg/kg oral Osveral daily and second group receive 40-50 mg/kg subcutaneous Desfereal for six nights a week. Complete blood count, serum levels of ALT, AST, ferritin, creatinine, and urinalysis were measured in both groups. Osveral drug was taken by patients once a day on an empty stomach at least half an hour before a meal. Exclusion criteria included serum creatinine increased by more than 33% compared to baseline, vision and hearing problems, hyperemesis, lack of response to anti-nausea medication and fluids therapy, severe and rapidly progressive skin rash, increase in liver enzymes more than 5 times normal, platelets less than 150 thousand, and neutrophils less than

1,500. Patients were visited weekly on the base of drug tolerance and side effects and the results were recorded on the form.

Statistical analysis

These data were analyzed by Spss16 statistical software, chi-square test and t-test. P. value<0.05 was considered as significance level.

RESULTS

In this clinical trial study, 138 patients were studied in two groups; Osveral and Desfereal that 62 (44.9%) were male and 76 (55.1%) were female. Among the patients, 122 cases (88.4%) had major thalassemia and 16 cases had intermediate thalassemia. The average age of patient's was13.59±6.81 which ranged from 4 years to 27 years and the average weight was 26.73±11.14 kg (maximum 55 and minimum 10 kg). Before the study, the mean hemoglobin level was 9.47±1.39 mg/dL ranged from 6.5 to 13.6. White blood cell count, platelet count, and creatinine were normal in all patients before the study and there was no significance difference between two groups. Patients in this study were divided into two groups; 69 cases in Osveral group and 69 cases in Desfereal group.

Table 1 shows the gender and type of thalassemia in two groups. The average age of patients in Osveral group was 13.29±7.44 and in Desfereal group was 13.9±6.17 and there is no significance difference statistically (P.value=0.602). The average weight was 25.17±10.56 kg in Osveral group and 28.29±11.56 in Desfereal group and this difference was not statistically significant (P.value=0.199).

Patient test results are shown in Table 2 before the study. This table shows that there is no significance difference between two groups in based on test results. The hemoglobin level of all patients was reduced from 9.47±1.39 at the beginning of study to 8.99±1.02 at the end of study that showed this difference is significant (P.value<0.001). The ferritin level was significantly decreased from 2760.25±1410.91 at the beginning of study to 2522.12±1232.85 at the end of the fourth month and to 2200.56±1032.05 at the end of study in total patients (P.value<0.001).

Table 3 shows a comparison of the ferritin level in different time periods. Comparison of hemoglobin and ferritin reduction at the beginning, end of forth month and end of study shows in table 4. Finally leukopenia was seen in 3 cases (2.2%) and thrombocytopenia in 5 patients (3.6%) in view of side effects in both groups (table 5).

Table 1. Comparison of gender and type of thalassemia in two groups

Items	Sex	Osveral	Desfereal	P. *value*
Gender	Male	30(43.5%)	32(46.4%)	0.432
	Female	39(56.5%)	37(53.6%)	
Type of thalassemia	Major	60(87%)	62(89.9%)	0.396
	Intermediate	9(13%)	7(10.1%)	

Table 2. Test results of patients in two groups before the study

Items	Group	Average	Standard deviation	P.value
Hemoglobin	Osveral	9.6	1.49	0.49
	Desfereal	9.35	1.29	
White blood cell count	Osveral	3646.49	1694.30	0.622
	Desfereal	3795.79	1852.02	
Platelet count	Osveral	310376.81	137824.81	0.912
	Desfereal	312942.02	133814.71	
AST	Osveral	39.49	15.96	0.247
	Desfereal	36..31	16.08	
ALT	Osveral	42.89	24.22	0.149
	Desfereal	37.31	20.81	
Creatinine	Osveral	0.55	0.11	0.446
	Desfereal	0.53	0.17	
Ferritin	Osveral	2839.97	1624.06	0.509
	Desfereal	2680.52	1166.25	

Table 3. Comparison of the ferritin level in different time periods

Items	Group	Average	Standard deviation	P. *value*
Ferritin level at the beginning of study	Osveral	2839.97	1624.06	0.509
	Desfereal	2680.52	1166.25	
Ferritin level at the end of forth month	Osveral	2584.26	1383.74	0.556
	Desfereal	2459.97	1067.52	
Ferritin level at the end of study	Osveral	2248.20	1130.11	0.589
	Desfereal	2152.91	929.61	

Table 4. Comparison of hemoglobin and ferritin in both group

Items	Group	Average	Standard deviation	P.value
Hemoglobin reduction from beginning to end (g/dl)	Osveral	0.71	1.24	0.011
	Desfereal	0.25	0.83	
ferritin reduction from beginning to forth month (µg/L)	Osveral	225.71	834.27	0.793
	Desfereal	220.55	736.60	
ferritin reduction from froth month to end (µg/L)	Osveral	336.05	630.10	0.782
	Desfereal	307.05	595.27	
The overal reduction in ferritn from beginning to end (µg/L)	Osveral	591.76	903.87	0.666
	Desfereal	527.60	835.72	

Table 5. Comparison of side effects in both groups

Side Effects		Osveral	Desfereal
Leukopenia	No	66(95.7%)	69(100%)
	Yes	3(4.3%)	0(0%)
Thrombocytopenia	No	65(94.2%)	68(98.6%)
	Yes	4(5.8%)	1(1.4%)

Leukopenia : white blood cell less than 1500; Thrombocytopenia: Platelets less than 150,000

DISCUSSION AND CONCLUSION

We showed that hemoglobin and ferritin level significantly decreased with Osveral and Desfereal therapy in both groups. Reduction of the amount of iron in the blood and liver with these drugs has been approved in many studies. Since both the drug has been approved by America's Food and Drug Agency (FDA), Therefore, many studies has been done on the effects of the two drugs in serum iron chelators and Almost all studies have reported a significant effect of these drugs (Berdoukas et al., 2011; Kanda et al., 2011; Galanello et al., 2010; Taher et al., 2009; Neufeld., 2006). A number of studies have compared the efficacy of these two drugs. Kanda et al. (2011); Taher et al. (2009); Mcleod et al. (2009); Neufeld (2006); Federico et al. (2009); Cappellini et al. (2006) have been introduced the drug Deferasirox as better option for patients receiving chronic transfusion therapy in their studies. The Mcleod et al. study (2009) showed that the Deferasirox more affordable than Deferoxamine because it is orally and has a longer half-life that makes it easier to tolerate. In this study concluded that the Deferasirox is more effective than Deferiprone in the younger age. However, Vichinsky et al. study (2007) showed that Deferasirox and Deferoxamine have a similar effect in sickle cell disease receiving blood transfusions and there is no significant difference between frequent blood recipients in view of reducing serum ferritin with both drugs. Deferoxamine was very effective in reducing serum iron in Kalpatthi et al. study (2010). In a number of studies, researchers have been proposed more effective combination therapy for iron chelators. The study of side effects in this study showed not significant effects after taking these drugs. In this study it was found that leukopenia was observed only in 2.2% and thrombocytopenia in 6.3% of patients that this number was not statistically significant. In Federico's study was seen the Deferasirox is well tolerated and side effects is not significant. The listed side effects for this drug was nausea, vomiting, diarrhea, abdominal pain and skin rash however, increased levels of liver enzymes and serum creatinine were not observed (Federica et al., 2009). Cappellini et al. (2006) observed a mild increase in creatinine level in his study but Deferasirox was well tolerated by patients and significant impact on reducing the amount of liver iron and serum iron. In another study, Deferasirox is been more effective than Deferoxamine (Cappellini, 2007). In Vichinsky et al. study (2007) conducted in patients with sickle cell, side effects such as nausea, vomiting and abdominal pain for Deferasirox was reported. But the researchers noted that mild increase of creatinine and liver enzymes has occurred after taking Deferasirox. Treatment in 11.4% of patients in Deferasirox group and 11.1% in Deferoxamine group was discontinued because of side-effects in this study .

According to obtained results from our study, it appears that iron chelators like Desfereal and Osveral are vital in transfusion-dependent patients. Although the special side effects were not observed for these two drugs but given that the Desfereal is an injected drug and the other hand it has a short half-life and the need to inject more than once a day, Therefore, patients were more likely to use an oral medication such as osveral.

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