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Combined Deferoxamine - Deferasirox in Treatment of Thalassemia Major with Iron Overload

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ABSTRACT:

Background Iron overload is a major problem to thalassemia major patients. For the treatment of those patients, there is an important role played by the effective and safe iron chelating protocol with high compliance rate. This prospective comparative study was conducted for the assessment of the deference in the response of serum ferritin and safety of combined Deferasirox (DFX) - Deferoxamine (DFO) therapy and deferasirox (DFX) protocol in a group of transfusion-dependent thalassemia major patients in Najaf thalassemia center, Iraq.

Material and Method Forty two patients were studied, aged between 2 to 30 years old, mean SD (8±3). Patients divided in to two groups, 29 patients chosen randomly on DFX (40 mg/kg/day), and 13 patients were willing to continue combined therapy of DFO(20mg/kg/day infusion ,two days /week) and DFX.The duration of study was one year. Efficacy of both regimes determined by assessment of serum ferritin level before and after treatment in both group, and the safety assessed by frequent monitoring of liver enzymes , blood urea and serum creatinine.

Results After one year of therapy, patients on DFX alone have shown significant reduction of serum ferritin from mean (4482±452) range (1148-10450 ng/l), to mean of serum ferritin (3132±336) range (595-8743 ng/l) No significant changes were observed in this study regarding blood urea and liver enzymes, but fortunately there was a decline in (ALT), from mean value of (82±16), to mean value (56±6).

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Introduction

Chronic blood transfusion is always required to treat hemoglobinopathies such as sickle cell anemia and thalassemia. If they are left untreated, then iron over load may lead to severe morbidity (such as liver damage, cardiac disease, diabetes, osteoporosis) and early mortality. [1]

Iron overload is an inevitable problem in major thalassemia patients. There is about (200 – 250) mgs of iron in each unit of packed blood [2-3]

The body has no active mechanism for accumulated iron excretion [4]. Iron overload may result in tissue and organ damage such as cardiac failure, hepatic diseases, endocrine disturbances, all of which may eventually lead to death [5-6].

There have been established evidences that iron chelating drugs reduce tissue damages and improve life expectancy in these patients [7] , who need continuous iron chelating drugs. The aims of iron chelating therapy in these patients are; first, reducing iron burden, secondly, reducing risk of tissue damage especially in specific key organs such as heart and liver, thirdly, improve life survival, fourthly, provide 24 hours protection against the toxic impacts of iron such as Labile Plasma Iron, and finally, reduce gap free of iron chelating drugs [8].

Till now, deferoxamine or (DFO) has been considered the treatment of choice for chronic iron overload patients [9].

Multiple different iron chelating regimens have been used recently, including monotherapy, combined and alternative sequential regimens [10-11].

Deferasirox is an iron chelating drug which is taken orally, and has been developed to manage transfusion overload of iron. Treatment of thalassemia major patients with deferasirox has shown its efficacy to decrease iron burden as well as its tolerability and safety.

The compliance between oral administration of deferasirox and parenteral administration of deferoxamine has proven challenging to all thalassemia major patient groups who are suffering from transfusion over load [12]

Material and Method

This prospective, comparative study done in AL Najaf

thalassemia center, from January 2011, until the end of January 2012. Thalassemic Patients enrolled in this study were 42 of transfusion dependents.

Twenty nine (29) patients were chosen to start oral (DFX) therapy randomly by way of (2:1) sequence of their files .Starting oral dose was 30/mg/kg day, before breakfast, increased gradually by 5mg/kg/month to maximum of 40 mg/kg/day.

Thirteen (13) patients were already on (DFO) therapy on a dose of 20 mg/kg/day, subcutaneously infused by special portable device, 12 hour a day, five days /week. When they were chosen to enter this study, their therapy changes to combined (DFO) 20mg/kg/day infusion two days per week, and (DFX) in dose of 40 mg/kg/day seven days per week.

Written consents were taken from patients or parents who chose combined therapy, and the draw back of each drugs were clarified for all patients in both group.

Serum ferritin level of those who were on DFX alone at the start of the study was in the range (1148-10450 ng/ml), while ferritin level of those who chose combined therapy, at the start of the study, was in the range (6175-10800 ng/ml).

For all studied sample, Cell Blood Count (CBC), serum ferritin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), BUN, urinalysis, visual and auditory examination and echocardiography were tested before treatment and each month throughout the treatment period.

Patients with serum creatinine above the upper normal limit and patients with active hepatitis were excluded from the study.

Safety of both drug regimens was monitored by monthly assessment of liver enzymes. Blood urea, serum creatinin level and prothrombine time.

The SPSS 16.0.2 program was applied for the statistical analysis of data. Differences were considered significant at ($P < 0.05$).

Results

No significant adverse effect was found in both drug regimens, leading to discontinuation of treatment & there was no patient loss during one year follow up. Haemoglobin level of all patients was maintained between (8.6-9.8gm/dl).

Adverse side effects which occurred in only(7)patients(17.5%)receiving

either treatment, are notified, these events observed in four(4)patients taking DFX, and in three patients taking combined DFO-DFX therapy.

These adverse events include: some bouts of abdominal pain, diarrhea, cough, itching, and back pain. Flu like illness was noticed in two patients on combined therapy, which may be related to exposure to cold during winter.

Regarding alanine aminotransferase (ALT), level fortunately showed some decline in those who were on monotherapy (82±16 IU/l) at the start and 56±6 IU/l at the end), P value was not significant, while in those patients who were on combined therapy, slight elevation of ALT (62 IU/l) to (68 IU/l) was noticed after one (P-value was not significant) {table}

For those who were on combined therapy, no significant difference in the ALT levels was observed at the end of the study.

Regarding prothrombine time (PT) and aspartate aminotransferase(AST) in both group, all reading were maintained within permitted levels ,and there was no significant surge noticed for all reading, p value was not significant for the mean SD in both groups.

Serum creatinine (SC) and blood urea (BU) level maintained within normal level, meansSD, were (0.4±2 and 27±3) respectively, for both groups. [table1]

Forty two (42) patients were chosen to enter both type of treatments,29 patients continued on oral DFX ,at the start, their serum ferritin range from(1148-10450ng/ml), mean±SD (4482±425 ng/ml). At the end of our study, the mean serum ferritin was reduced to mean±SD (3132±336) with a range (595-8743 ng/ml).[table1]

Table 2;demonstrate that the mean pair deference between mean serum ferritin level at the start ,and its mean level at the end of the study was(1350±227), confidence interval (95%) of which, lies between serum ferritin level (884-1815) and the p-value is statically very significant(0.001).

Thirteen patients (13) chosen randomly for combined DFO-DFX therapy. Serum ferritin range was (6175-10800 ng/ml), mean±SD (8601±352), at the end of the study, serum ferritin maintained between (4215-8934 ng/ml), mean±SD (6656±384)

and the p value is very significant.[table1]

Mean pair deference between the two serum ferritin means SD at the start and the end is (1945±277), with confidence interval (95%), lies between (1346-2544 ng/ ml)[table3]

Those patients, who were on combined therapy, demonstrated more reduction in serum ferritin (1945±277 ng/ ml)[table3] than those who were on deferasirox alone (1350±227 ng/ ml) and p value was statically significant (0.01).[table 2]

Table 1; changes in deferent variable over one year for patients in both groups

	variable over one year for patients on DFX				variable over one year for patients on combined therapy		
	variable	Mean	no	Std. Error Mean	Mean	no	Std. Error Mean
Pair 1	sfer1	4482.9310	29	425.36411	8601.5714	13	352.446
	sfer2	3132.7241	29	336.17471	6656.0714	13	384.644
Pair 2	BU1	30.5172	29	3.03102	27.5714	13	2.3457
	BU2	28.4310	29	2.03513	26.7143	13	1.6152
Pair 3	ALT1	82.5517	29	16.05813	62.4107	13	0.463
	ALT2	56.4138	29	6.53477	68.4500	13	0.066
Pair 4	AST1	91.9310	29	12.88142	49.1429	13	4.036
	AST2	93.5172	29	13.15038	56.7857	13	6.238
Pair 5	PT1	13.8966	29	0.20064	12.1429	13	0.3315
	PT2	13.1379	29	0.48047	13.0000	13	0.7875
Pair 6	SC1	0.421	29	0.001	0.4107	13	0.014
	SC2	0.502	29	0.021	0.4500	13	0.021

(1)=start of therapy (2)=At the end of study (pt)prothrombine time (SC) creatinin-(BU)blood urea---(S Fer) serum ferritin.

TABLE 2; paired sample test for mean SD of all variable at the start and end of study for patients on DFX treatment

	Paired difference	95% confidence interval of difference		t	pt	Sig(2-tailed)
		Lower	upper			
S Fer 1 – S Fer 2	1350.206	884	1815	5.9	29	**0.00**
BU 1---BU 2	0.0862	-0.021	-194	1.636	29	**0.113**
ALT1 --ALT2	26.137	15.906	-6.444	1.643	29	**0.112**
AST1—AST2	-1.586	5.957	-13.7	-0.266	29	**0.792**
PT1—PT2	0.7586	0.5077	-.2813	1.494	29	**0.146**
SC 1 –SC 2	-0.180	0.301	0.422	0.238	29	**0.123**

TABLE 3; paired sample test for mean SD of all variable at the start and end of study for patients on DFO-DFX treatment

		Paired Differences					t	df	Sig. (2-tailed)
					95% Confidence Interval of the Difference				
		Mean		Std. Error Mean	Lower	Upper			
Pair 1	sfer1 - sfer2	1945.5		277.2	1346.6	2544.3	7.018	13	.000
Pair 2	buu1 - bu2	.85714		2.53732	-4.62440	6.33869	.338	13	.741
Pair 3	aip1 - alp2	-.403929		.07777	-.20731	.12874	-.505	13	.622
Pair 4	gpt1 - gpt2	-7.64286		9.21275	-27.54580	12.26008	-.830	13	.422
Pair 5	pt1 - pt2	-2.42857		7.41080	-18.43863	13.58149	-.328	13	.748

Discussion

For transfusion-dependent thalassemic patients, iron chelation therapy is lifelong requirement , but till now, there was limited published data, from prospective clinical trial in pediatric patient's clarified efficacy and safety of long term treatment. Since 1970s, deferoxamine or (DFO) has been the standard iron chelating drug, and it is safe and effective in transfusion hemosiderosis. The hexadentate chelator binds with iron tightly, and the DFO-iron complex is excreted in both stool and urine. Monotherapy with Deferoxamine needs an electronic pump to slow infusion over (8-12) hours, and (5-7) nights weekly [13]. So, for long period patients were not complied well with lifelong subcutaneous therapy. [14,15].

The other iron chelator drug is Deferasirox, with a half life time of (8-16) hours, and similar to DFO, it can't provide 24-hour chelating coverage. Monotherapy have not achieved all therapeutic goals because of short half lives of these medicines (20-30 minutes for DFO and 8-16 hours for Deferasirox) and rapid decline in plasma levels.[13] Over the long period of time, deferasirox has been generally well tolerated in both adult and pediatric thalassemia patients. Deferasirox is an iron chelating agent that is administrated once-daily orally, and has proven to be effective in lowering liver iron levels and serum ferritin concentrations over one year in transfusion-dependent anemic patients.[16]

There was limited published data that highlight the efficacy and effect of combined usage of oral iron chelator deferasirox and subcutaneous deferoxamine, although there was no apparent drawback of using both drugs since each compound has different way of metabolism and elimination from the body.

Regarding the safety of oral chelator, Rheault MN ea al had reported Fanconi-like syndrome in the kidneys during treatment with deferasirox [17], a condition which was not reported in our study, nevertheless, its safety regarding effect on serum creatinine and blood urea was very clear in this study, even with sustained dose of deferasirox (40mg/kg/day) throughout one year period.

Although it is known that deferasirox had tendency for liver enzyme elevation, particularly in

patients with high liver iron concentrations [18], in our study its effect on liver enzymes was not significant, on the contrary there was some improvement in AST, as shown in table 2.

Cohen AR, notified that, none of iron chelator drugs could provide all therapeutic goals in transfusion dependent thalassemia patients based on monotherapy approach.[19] Our study demonstrated significant change in serum ferritin, throughout one year period, the mean SD of serum ferritin level reduced from (4482±425 ng/ml) to (3132±336 ng/ml) with p-value 0.001.

Combined DFO (20 mg/kg/day, 2days/wk) and DFX therapy(40 mg/kg/day , and 7 days weekly) have shown maintained significant and safe decline in mean serum ferritin (8601±352) to (6656±384 ng/ml) with no clear changes in hepatic or renal function. Combination therapy first practiced in major thalassemia by Anderson et al. They used combination Deferoxamine / Deferiprone and proposed several potential advantages with this regimen [20]. Medicines with different properties and mechanisms may access different iron pools.

The molecule of Deferasirox is small and can easily enter into cells and is able to transfer iron into plasma for Deferoxamine chelation.[21] This approach of therapy is a flexible regimen, which would allow the clinicians to reduce the nightly Deferoxamine injections and increase the oral doses with high efficacy and low toxicity. In present study serum ferritin decreased significantly in both groups of studied patients. Combined regimen was associated with minimal adverse effect as it was showed by insignificant changes in liver enzymes, PT, BU and Serum creatinine.

Keikhaei Bd had shown significant elevation of serum creatinine in 21% of patients studied with sequential DFO-DFX regimen, although creatinine rising were in normal limits. It was reported that in monotherapy approach this adverse drug reaction is high. [22] Combined oral deferiprone-subcutaneous deferoxamine had shown significant improvements in in cardiac function in thalassemia patients with heart failure. [23]

Our study revealed a significant variation in mean serum ferritin

between its level at the start, and at the end of the study in both studied groups ,but still those who were on combined therapy, demonstrated more reduction in serum ferritin(1945±277 ng/ml) than those who were on deferasirox alone (1350±227 ng/ml) and p value was statistically significant(0.01). In spite of this result still we maintained our confidence in oral chelator since it was associated with excellent compliance , least disturbance in daily activities and without pain associated with injection even with two days per week protocol in this study.

Lal A et al clarified that administration of DFX and DFO simultaneously has rapidly decreased the myocardial and systemic iron, and provided an excellent control on the toxic labile plasma iron species without increasing their toxicity. Their clinical trial was conducted to assess the efficacy and safety of combined treatment with deferasirox (DFX, 20-30 mg/kg/day) and deferoxamine (DFO, 35-50 mg/kg on 3-7 days/week) in 22 thalassemic patients who have persistent iron overload or organ damage [24].

Combined Deferoxamine - deferasirox are a new protocol to date with advantages of more time iron chelator coverage, acceptable efficacy and compliance and lower side effects. This new protocol still needs more clinical trials to be performed on larger target groups in order to insure its safety and efficacy, so that perfect benefit insured for those patients with iron overload with serious life threatening complications.

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