

Serum ferritin and liver function test response to oral versus subcutaneous iron chelating agent

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Abstract: *Thalassemias are group of inherited autosomal recessive blood disorder. The genetic defect, which could be either mutation or deletion, results in complete absence or reduction synthesis of one of the globin chain that make up hemoglobin. This cause reduction of haemoglobin molecules production ,resulting in decreased of oxygen carrying capacity of the circulation thus causing anemia, the characteristic presenting symptom of the thalassemia. Good chelation therapy and regular blood transfusion protocol have increased the life expectancy.*

Objectives : *is to compare serum ferritin level and liver function test in a group of patients with beta thalassemia major in response to subcutaneous and oral chelating agent .*

Patients and Methods: *Prospective analytic study design done on group of 60 patients with beta thalassemia major diagnosed by hemoglobin electrophoresis registered in thalassemia center in AL – Zahra Teaching Hospital for Maternity and Children in AL- Najaf AL-Ashraf , during a period from*

1st of February 2019 to 1st of February 2020, aged 2.5 to 17.9 years with serum ferritin levels above 1000 ng/ml and liver transaminases below 5 folds the normal upper limit .

The patients divided into 2 groups, 30 patients were on Deferasirox {Exjade} therapy and 30 patients were on Deferoxamine {Desferal} therapy .

Base line S. Ferritin value as well as LFT (S. GOT , S. GPT , ALP and TSB) value, were taken as base line level and then every (8-12) weeks and were used to assess the changes that occurred in response to subcutaneous and oral chelating agent .

Results : *Our study show significant decline in SF (P value <0.05) in both groups after 1 year of treatment with oral or subcutaneous chelating agent. Patients on Exjade show more rate of decrement of serum ferritin (11%) compared to patients taken Desferal who a rate of decrement (6%). Patients on Exjade and Desferal therapy show increment in liver enzymes after 1 year of treatment with statistically significant results, p-value < 0.05 .*

Conclusions

We found superiority in oral iron chelating agents (Exjade) to subcutaneous iron chelating agents (Desferal). Serum ferritin level is suitable for long term monitoring as an indicator of efficacy than liver biopsy .

Keywords: *Thalassemia, Deferasirox, Deferoxamine, chelation, serum ferritin, liver function test.*

1. INTRODUCTION:

Beta thalassemia syndromes are inherited diseases caused by a genetic defect in the synthesis of beta-globin chains of hemoglobin. In individuals with B-thalassemia, the B-globin chain is either completely deficient or partially reduced. Thalassemia major occur when there is homozygous state resulting in very severe anemia which required chronic blood transfusion. Thalassemia minor occur in the heterozygous state leading to mild to moderate anemia.[1]

Treatment of B-thalassemia major required lifelong regular blood transfusion to maintain Hb between 9.5 to 10.5 g/dl.[2] Each 100-200 ml of pure RBC/kg/year, are equivalent to 116-232 mg of iron/kg/year.[3] This causes iron overload in the body which required regular chelation. There are two commonly used chelation agents; deferoxamine and deferasirox.

Deferoxamine (Desferal) is given subcutaneously over 10–12 hr, 5–6 days a week at a dose of 20-40 mg/kg/day.[4] Approximately 8 mg of iron is bound by 100 mg of deferoxamine.

Deferasirox (exjade) is an orally active chelator that is highly selective for iron, excreted by liver. The recommended dose of Exjade is 20-40 mg/kg once daily taken on an empty stomach at least 30 minutes before breakfast, absorbed following oral administration with a median time to peak plasma concentration of about 1.5 to 4 hours.[5]

Liver function should be monitored every month and the chelating drug should be discontinued if there is a persistent and progressive increase in serum transaminase levels that cannot be attributed to other causes.[6]

Ferritin is the main iron carrying protein in the body so it can be used to indirectly assess the iron level in the body tissues. It is resemble good however not 100% reliable indicator of iron body store.[7]

2. AIM OF THE STUDY

Is to compares the changes in the serum ferritin level and liver function test in a group of patients with beta thalassemia major in response to subcutaneous and oral chelating agent.

Patients and Methods:

This is intersectional descriptive study was done on group of 120 patients with beta thalassemia major diagnosed by hemoglobin electrophoresis & registered in thalassemia center in AL - Zahra Teaching Hospital for Maternity and Children in AL- Najaf AL- Ashraf city ,during a period from 1st of February 2019 to the 1st of February 2020, aged 2.5 to 17.9 years with serum ferritin (SF) levels above 1000 ng/ml, or with a history of multiple transfusions (>10 transfusions), and liver transaminases level below 5 folds the normal upper limit (NUL).

Other inclusion criteria were normal complete blood count, negative serologic tests for HCV, HBV and HIV, normal serum creatinine level, no proteinuria in urine analysis, no cardiac problem neither taking any cardiac drug and finally no auditory or ophthalmologic problem. Any patient with data or information against the mentioned above did not include in this study.

Sixty patients (50%) were put on Exjade (who could not tolerate subcutaneous iron chelating as they need dose greater than 30 mg/kg) and another 60 patients (50%) were on Desferal therapy. Each patient comprehensively informed about the study and also their rights to withdraw from the study whenever they wished.

Following parents' consent, blood is typically drawn from a vein by a needle with syringe after antiseptic technique. Blood samples (6cc) were taken for evaluating : Serum ferritin and Liver function test: which include S. GOT, S. GPT, ALP and TSB.

Baseline serum ferritin as well as LFT were taken prior to the start of treatment and then were assessed every 8-12 weeks.

More than 5 fold increase above the normal serum transaminase level was considered as severe liver dysfunction and indicated transient or permanent discontinuation of the drug .

Statistical analysis

Statistical analysis was done using SPSS program version from IBM version 21. Median, mean and standard deviation were measured for quantitative data, ANOVA, T test and chi square were used to assess the hypothesis significance. P value regarded as significant when it is less than 0.05.

3. RESULTS

Table 1 :

Distribution of Thalassaemic Patients According to Gender.

	NO.	%
Male	70	58.3%
Female	50	41.7%

Table 2:

Effect of Either Exjade or Desferal on S. Ferritin Decrement, Throughout One Year Treatment in Thalassaemic Patients for Both Drugs with Three Months Interval.

	Baseline level	%	After 6 months	%	After 12 months	%
Exjade	1962±554	4.2	1880±529	9.5	1702±494	11
Desferal	1645±535	4.9	1565±530	64,8	1490±412	6

Showing there is more rate of decrement of SF after 12 months of treatment on patients taken Exjade with rate of decrement (11%) while patients taken Desferal Show rate of decrement (6%) in the same period. Both drugs yield statistically significant results p value <0.05 .

Table 3 :

LFT Changes Throughout One Year Treatment on Both Drugs.

	NO.	No change in LFT		LFT<2fold		LFT≥2≤4fold		LFT>4fold	
		No.	%	No.	%	No.	%	No.	%

Exjade	60	24	40	26	43.3	6	10	4	6.7
Desferal	60	18	30	16	26.7	18	30	8	13.3
Total	120	42	35	42	35	24	20	12	10

patients on Exjade therapy have no change in LFT in 24 patients (40%), elevated LFT less than 2 fold of normal range in 26 cases (43.3%) and equal or more than 2 fold but less than 4 fold in 6 cases (10%) and more than 4 fold increment in LFT in 4 patients (6.7%). Statistically significant results, p- value < 0.05 .

Regarding Desferal therapy no change in LFT 18 patients (30%), elevated LFT less than 2 fold of normal range in 16 cases (26.7%) and equal or more than 2 fold but less than 4 fold in 18 cases (30%) and more than 4 fold in 8 patients (13.3%). Statistically significant results, p-value < 0.05.

Table 4:

S. GPT, S.GOT, ALP, TSB Changes, Throughout One Year Treatment in Thalassemic Patients on Exjade Treatment.

	Baseline	6 months	12 months	p-vaue
S.GPT(u/l)	55.3±17.4	78.9±19.4	86.5±16.3	P=0.451
S.GOT(u/l)	57.7±26.8	58.2±19.1	60.2±19.6	P0.123
S.ALP(u/l)	373±44.7	412±51.9	446±38.6	P=0.05
TSB	2.3±1.2	2.4±1.4	2.5±1.5	P=0.2

Table 5 :

SGPT, SGOT, ALP, TSB Changes, Throughout One Year Treatment In Thalassemic Patients On Desferal Treatment.

	Baseline	6 months	12 months	p-value
S.GPT()	63±18	74±16	79±19	P=0.04
S.GOT()	42±13	57±22	73±24	P=0.02
S.ALP	337±65	412±31	439±28	P=0.01
TSB	0.7±2.5	0.6±2.7	0.4±2.8	P=0.07

4. DISCUSSION

Regarding patients on Exjade therapy, show significant decline in SF ,(P value <0.05), as mean baseline serum ferritin (SF) was 1962±554 ng/dl and after 1 year of treatment mean serum ferritin (SF) became 1415±302 ng/dl with rate of decrement about 27.9%. This result can be explained by that; serum ferritin is an indicator of iron overload but also an acute phase reactant protein so decrement in serum ferritin may reflect a chelating effect of deferasirox or a possible anti-inflammatory effect of deferasirox or both effects.[8]

This result similar to the study done in Greece [9], that show Deferasirox produced a significant reduction of mean serum ferritin levels after 12 months of treatment from $1,989\pm 923$ to $1,008\pm 776$ ng/dl, ($P<0.001$). Another study, Ali Taher [10], show that Deferasirox at doses of more than 30 mg/kg/day decreases the serum ferritin to below the levels prior to dose escalation by 487 ng/dl, ($P<0.0001$). Mean of Relative Changes of serum ferritin was 14.2%. Another study done in Iran [11], showed significant decline in SF during one year of iron chelating therapy with Exjade, (P value <0.001). Mean of relative changes of serum ferritin was 38.9 ± 11.4 % .

Regarding patients on Desferal therapy, show significant decline in SF, (P value <0.05), after 1 year of treatment as mean baseline serum ferritin was 1645 ± 535 ng/dl and after 1 year of treatment the mean serum ferritin became 1352 ± 254 ng/dl with rate of decrement about 17.9%. A study done in Italy [12], showed that over the study duration, mean serum ferritin levels remained stable in the Desferal groups.

Regarding LFT changes, patients on Exjade show increment of liver enzymes during 1 year of treatment with Exjade but does not reach level of more than 5 fold and also does not lead to transient or permanent discontinuation of the drug. Statistically significant results, p -value < 0.05 . This result can be explained by cellular toxicity caused by chronic deposition of iron, although the exact pathophysiologic mechanism for hepatocytes injury and liver fibrosis are not completely clear. These include peroxidation of organelle membranes, increased lysosomal fragility and decreased mitochondrial oxidative metabolism. [13]

Ali Taher [10], this study show that, 9 patients (3.4%) had ALT levels of >5 ULN (upper limit normal) but <10 ULN at two consecutive assessments at least 7 day apart. Another study done in Iran [11], showed that serum transaminases, (ALT and AST), were elevated more than 5 fold of normal range in 24 (5.89%) cases, which led to temporary or permanent discontinuation of drug.

Regarding Desferal therapy in our study, no change in LFT in 9 patients (30%), elevated LFT less than 2 fold of normal range in 8 cases (26.7%) and equal or more than 2 fold but less than 4 fold in 9 cases (30%) and more than 4 fold in 4 patients (13.3%) with statistically significant results, p - value < 0.05 .

A study done in Italy [12], show that most patients had normal AST levels at baseline, though a some percentage (32%) had raised ALT, which may be due to liver damage caused by transfusion related viral hepatitis and/or iron overload. No patient developed consistent or progressive elevations in transaminase levels. Another study done in Italy [13], found similar increase in hepatic transaminase level in patients with Desferal dose of 30 mg/kg and apply this increment to the iron toxicity itself rather than Desferal therapy itself since it is mainly excreted in urine.

5. CONCLUSIONS

We found superiority in oral iron chelating agents (Exjade) to subcutaneous iron chelating agents (Desferal). Serum ferritin level is suitable for long term monitoring as an indicator of efficacy than liver biopsy.

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