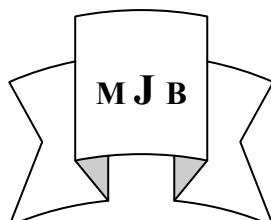


Changes of Some Liver Function Tests with Regular and Irregular Desferroxamine Therapy in β -Thalassemic Patients

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Abstract

Objectives: (a) To determine the effect of regular desferroxamine (DFO) therapy on De-Ritis ratio. (b) To determine the changes in some liver function test parameters between patient on regular DFO and those with irregular DFO therapy. (c) To determine the relation between serum iron and serum ferritin in both groups. (d) To determine the effects of age, sex and body mass index (BMI) on measured parameters in both groups.

Subjects and Methods: This study was conducted at Thalassemia Center /Ibn-Al-Atheer Pediatric Hospital in Mosul from October 2007 to April 2008. Forty patients with β -Thalassemia were selected as follow: twenty patients with regular DFO therapy and other twenty with irregular DFO therapy.

Results: De-Ritis ratio serum Ferritin, Ferritin: total serum protein ratio and total serum protein show no significant changes between both groups. Serum ALT, AST, ALP activities and serum iron show a significant increase in those with irregular DFO therapy [$P < 0.01$].

Conclusion: Irregular DFO therapy shows significant effects on serum iron and some other liver function test parameters that indicate chronic hepatocytes damage without changes in De-Ritis ratio which is used as an indicator for acute hepatocytes damage.

الخلاصة

أهداف الدراسة : بيان تأثير الانتظام في المعالجة بالديسفيروكزامين على قيمة دي-راتز و التغيرات الحاصلة لبعض معايير فحوص الكبد للمرضى المنتظمين على العلاج وأولئك الذين لا ينتظمون باستخدام العلاج وكذلك إيجاد الارتباط بين تركيز الحديد في الدم مع تركيز الفريتين. إضافة إلى ذلك شملت الدراسة توضيح تأثيرات عملي العمر ومعامل كتلة الجسم على المعايير المقاسة.

طرق العمل : أنجزت هذه الدراسة في مركز الثلاسيميا /مستشفى ابن الأثير للأطفال في الموصل للفترة من كانون الأول ٢٠٠٧ ولغاية تموز ٢٠٠٨. اختير أربعون مريضاً مصاباً بالثلاسيميا و توزعوا كما يلي عشرون مريضاً منتظمين على العلاج بالديسفيروكزامين وعشرون من غير المنتظمين على العلاج. تم تحليل البيانات باستخدام اختبار-t كما قيس تأثير كل من العمر و الجنس ومعامل كتلة الجسم على المعايير المأخوذة بواسطة معامل الارتباط .

النتائج: لم تظهر كل من نسبة دي-راتز وتركيز الفريتين نسبة الفريتين الى البروتين الكلي و البروتين الكلي تغيراً ملحوظاً بين المجموعتين في حين اظهر تركيز الحديد في الدم وفاعلية كل من الإنزيمات الفوسفات القاعدي و ALT و AST زيادة ملحوظة عند غير المنتظمين على العلاج (ب>٠,٠١).

الاستنتاج: يوجد تأثيرات ملحوظة لعدم الانتظام بالمعالجة بالديسفيروكزامين على تركيز الحديد و بعض معايير وظائف الكبد و التي تبين الضرر المزمن الحاصل في خلايا الكبد بدون أحداث تغير في نسبة دي-راتز و التي تستخدم كمؤشر للضرر الحاد في خلايا الكبد.

Introduction

A known consequence of regular blood transfusion in patients with β -thalassemia (BT) major is iron overload which is associated with injury to heart, liver and endocrine organs. Chelation therapy with desferrioxamine (DFO) for iron overload has been used to reduce toxicity. [1]

A high dose of DFO treatment, however may be complicated by neurotoxicity [2], skeletal muscle dysplasia and growth retardation. [3, 4, 5] The degree of iron overload is therefore important for the adjustment of chelating dose; because the liver is the largest iron-store. Liver iron concentration has been taken to represent total body iron store. [5] Hepatocytes damage that occurs due to secondary iron overload arising from the sustained condition of oxidative stress, [6]. Although hepatic iron excess is characterized by a low degree of inflammation and hepatocellular necrosis, this low necrogenic activity may initiate and promote progressive fibroclerosis, eventually cirrhosis. [6] Elevated serum activities of ALT and AST have been observed in thalassemic patients with iron overload. [7]

Regular dose of DFO reduces liver enzymes progressively and it may reach near the normal values. [8]

Many studies have correlated serum ferritin to serum iron and ALT activity in thalassemic patients and have used it as an index for sufficient DFO dosing. [7] This study aims to fill the gap in the knowledge concerning the effects of regular and irregular DFO regimen on hepatocellular injury in thalassemic patients with transfusional iron overload.

Subjects and Methods

This study was conducted at Thalassemia Center/ Ibn-Al-atheer

Pediatric Hospital in Mosul from October 2007 to April 2008.

Forty patients with β -Thalassemia major were selected as follow: twenty patients on regular DFO therapy and twenty on irregular DFO therapy. Both groups were under single blood transfusion/month with DFO dose of 40-60mg/kg/day for 5-6 days/week.

Serum iron was measured by Ferrozine method, [9] Serum Ferritin was assayed by Turbidimetry-Latex method, [10] ALT and AST activity were measured by Wootton and Freeman method, [11] ALP activity was measured by Kind and King method, [12] Total serum protein was assayed by Biuret method. [13]

De-Ritis ratio is considered as an index of acute liver injury and Ferritin: Total Serum proteins were calculated by equation as follow:

De-Ritis ratio = ALT / AST activity.

Fer./ TSP= Ferritin/ total serum protein

Data were represented as mean $\pm$ SD, 2-sample t-test and the effects of age, sex and BMI were obtained by Pearson- Correlation.

Results

De-Ritis ratio, serum ferritin, Ferritin: TSP ratio and total serum protein shows no significant changes between both groups. Serum AST, ALP activities and serum iron show a significant increase in patients with irregular DFO therapy ($P < 0.01$).

Serum iron was significantly correlated to Serum ALT activity and Serum Ferritin ($P < 0.01$) in patients with irregular DFO therapy, while in patients with regular DFO therapy serum iron were correlated to Serum AST and ALP activity ($P < 0.05$).

BMI correlated to ALP activity ($P < 0.05$) in those with irregular DFO therapy. Age and sex show no significant correlation to any of the

measured parameters in the studied patients.

In patients with regular DFO therapy, age correlation to Serum

Ferritin was highly significant ($P < 0.01$), sex and BMI show no significant correlation to any of the measured parameters.

Table 1 De-Ritis Ratio and Some Other Liver Function Test Parameters in Patients with Regular and Irregular DFO Therapy

	Parameters	Regular DFO therapy	Irregular DFO therapy
1	Serum Iron $\mu\text{g/dl}$	130.3 ± 15.2	$188.2 \pm 10.8^{***}$
2	Serum Ferritin $\mu\text{g/dl}$	1822 ± 270	1913 ± 273
3	De-Ritis Ratio	1.395 ± 0.167	1.420 ± 0.134
4	ALT-activity IU/L	52 ± 7.9	$71 \pm 11.3^{***}$
5	AST-activity IU/L	37.58 ± 6.83	$49.94 \pm 7.28^{***}$
6	ALP-activity IU/L	83.53 ± 8.21	$119.7 \pm 16.5^{***}$
7	Ferritin:TSP	$2.34 \pm 0.37 \times 10^{-4}$	$2.46 \pm 0.33 \times 10^{-4}$
8	TSP g/L	76.26 ± 4.31	75.95 ± 3.46

$P < 0.05 = *$, $P < 0.01 = **$, $P < 0.001 = ***$

Discussion

In the present study, De-Ritis ratio which was used as an indicator for acute hepatocytic damage shows no significant change in patients with irregular and regular DFO therapy and this can be explained by the fact that all patients present with chronic low grade inflammatory process that occur due to increased oxidative stress in the hepatocytes [6] and leading to cell membrane damage that is reflected as an increase in serum ALT and AST activities which end by fibrogenesis [14] and leading to non significant increase in De-Ritis ratio because both enzymes will increase in the same manner.

Fibrogenesis process leads to a significant increase in the serum ALP activity in those with irregular DFO therapy, due to positive iron balance and failure of Chelation therapy to stop Fonton reaction. [15]

The hepatocellular damage in thalassemic patients with irregular DFO therapy was assessed by aminotransferases activities and serum ferritin level. Irregular DFO patients show a significant increase in serum

activities of liver enzymes this can be explained by the fact that liver enzyme leaks from the cytoplasmic and mitochondrial compartments of injured hepatocytes to plasma. [16]

Serum ferritin decreases in a non-significant manner in patients with regular DFO therapy and this is due to the fact that regular DFO therapy will induce negative iron balance and so reduce iron body store. [17]

Serum Ferritin: TSP ratio shows non significant increase in those with irregular DFO therapy and this is due to irregularity of DFO therapy.[15]

Serum iron increase then increase the rate of Fonton reaction that associated with increase in the oxidative stress that aggravates the inflammatory process in this group of patients.[15]

In Conclusion: Irregular DFO therapy leads to a significant increase in serum iron and some liver function test parameters that reflect chronic hepatocytes damage without significant change in De-Ritis ratio which is used as an indicator for acute hepatocytes damage.

Recommendations

1. Patients should be educated and follow up for taking their DFO therapy and how to use their DFO pump.
2. Patient should be submitted to regular check for their iron status that include serum iron, serum ferritin, serum transferrin and saturation %.

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