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P-ISSN: 1687- 5788

e-ISSN: 1687- 7918

Original Article

Efficacy and Safety of a Short Term Iron Depletion Therapy in Hepatitis C Virus- Related Compensated Liver Cirrhosis

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ABSTRACT:

Background/Aim: The association of chronic hepatitis C and hepatic iron overload is known since more than a decade. Several studies have demonstrated that hepatic iron overload in patients with chronic hepatitis C is associated with a more liver pathology and a lower response to interferon therapy. Therefore, iron reduction therapy via therapeutic phlebotomy was tried in patients with chronic hepatitis C and was found to improve the biochemical and histological outcomes, and improve the response to interferon therapy. Recently, the potential role of (mild) increase of hepatic iron as a comorbid factor in mediating liver injury in chronic hepatitis C has been suggested and iron depletion therapy by phlebotomy has been found to produce beneficial results, regardless of the hepatic iron status. Although patients with HCV-related cirrhosis are more likely to have hepatic iron overload, the effect of iron reduction/depletion therapy on this group is not known. The aim of the study is to evaluate the efficacy and safety of a short-term iron depletion therapy by phlebotomy in HCV-related compensated Liver Cirrhosis.

Patients & methods: A prospective controlled pilot study, which included adult patients with evidence of HCV-related compensated cirrhosis, with elevated serum ALT levels and erythrocytosis. Twenty five patients fulfilled the study criteria, 16 of them (Group A) were intended to have therapeutic phlebotomy till mild iron deficiency anemia is induced and maintained for a period of 6 months, and 9 patients did not accept phlebotomy were used as a control group (Group B). The efficacy of therapeutic phlebotomy was evaluated on the basis of biochemical parameters and its safety by the clinical picture and investigations.

Results: Twelve patients of group A (75%) and 6 patients of group B (66.6%) had baseline serum ferritin levels more than the upper limits of normal. Three patients of group A were withdrawn from the study due to non-compliance. The mean number of phlebotomy sessions needed to induce iron reduction in group A was 9 ± 2 and to maintain it was 4 ± 2 . Phlebotomy significantly reduced serum ALT levels from 83 ± 8 to 42 ± 6 U/L; $P = 0.01$), with normalization of ALT levels in 10/13 (67.9%) of group A at the end of the study period. These changes were not observed in the control group. None of the patients developed ascites or other signs of hepatic decompensation during the period of the study.

Conclusion: The results of the present study demonstrate that a short term iron depletion therapy by phlebotomy is effective and safe in patients with HCV- related compensated cirrhosis and erythrocytosis.

Key words: Iron Depletion Therapy, HCV, Liver Cirrhosis

INTRODUCTION

Many patients with chronic Hepatitis C (CHC) and elevated aminotransferase activities have elevated serum iron levels, but only a minority of them has a hepatic iron overload⁽¹⁻⁶⁾. Several studies have shown that increased hepatic iron in patients with CHC is associated with a more liver pathology^(4,7), and a lower response to interferon (IFN) therapy⁽⁸⁻¹¹⁾, compared to patients with normal hepatic iron. These has been growing evidence that in patients with CHC, iron reduction therapy via therapeutic phlebotomy can lead to improved biochemical and histological outcomes⁽¹²⁻¹⁴⁾, as well as improved response to IFN therapy⁽¹³⁻¹⁶⁾, in spite of no consistent change in HCV RNA.

Although the association of CHC and hepatic iron overload is known since more than a decade, recently, a potential role of (mild) increase of hepatic iron as a comorbid factor in mediating liver injury in CHC has been suggested⁽⁶⁾. This agrees with the previous studies, which demonstrated that iron depletion therapy by therapeutic phlebotomy improved the response to IFN therapy, irrespective of liver iron status⁽¹⁷⁾. In addition, such response to IFN therapy was significantly higher in patients with lower hepatic iron deposits, even within the normal range. Interestingly, the hepatic iron content in IFN non-responders was far below that of iron overload⁽¹⁸⁾.

Although iron reduction/ depletion therapy has been found to be effective and safe in patients with CHC⁽¹²⁻¹⁸⁾, its effect on patients with HCV-related cirrhosis is not known. Importantly, those patients are more likely to have increased hepatic iron accumulation⁽¹⁹⁾. It has been shown that as many as 50% of HCV-positive cirrhotic patients have hepatic iron above the upper limit of normal⁽²⁰⁾, and they are more likely to have iron overload⁽²⁰⁾. This is contrary to patients with CHC, where hepatic iron overload was demonstrated in only 5-15%^(4,7). Therefore, patients with HCV-related cirrhosis might benefit more from iron reduction/depletion therapy.

AIM OF THE WORK:

Evaluation of the efficacy and safety of a short-term iron depletion therapy in HCV- related compensated liver cirrhosis

PATIENTS AND METHODS

A prospective controlled pilot study, including adult patients who fulfilled the following criteria:

A. Inclusion Criteria:

1. Evidence of HCV infection: Positive for ELISA-3 anti HCV antibody and PCR for HCV RNA.
2. Evidence of biochemical hepatitis: Elevated serum alanine transaminase (ALT) levels $\geq 1.5 \times \text{ULN}$ for ≥ 3 months.
3. Evidence of well compensated liver cirrhosis (Grade A Child-Pugh classification)⁽²²⁾, based upon the clinical picture, laboratory findings and abdominal ultrasound.
4. Evidence of erythrocytosis: Hematocrit values exceeding 55% for males and 50% for females.

B. Exclusion Criteria:

1. Evidence of leucopenia ($< 3,000/\mu\text{L}$), thrombocytopenia ($< 70,000/\mu\text{L}$) or anemia (hemoglobin $< 12.0 \text{ g/dL}$),
2. Evidence of iron deficiency (baseline serum ferritin $< 15 \text{ ng/mL}$)
3. Evidence of other concomitant diseases including HBV infection, HIV infection, alcoholic liver disease, nonalcoholic steatohepatitis.

Patients fulfilling the study criteria and accepted the study protocol were subjected to iron depletion therapy via therapeutic phlebotomy of 400 to 500 mL of whole blood every 1 to 2 weeks, according to the patients' response, until mild iron deficiency anemia has been induced,⁽⁶⁾ as defined by one of the following laboratory criteria: hematocrit $< 35\%$ or serum ferritin < 10

ng/mL. During the subsequent follow up, additional phlebotomies were performed if the hematocrit exceeded 35% or serum ferritin exceeded 15 ng/mL⁽⁶⁾.

During a -6 month period, patients of group A were followed every 2 weeks till iron reduction was achieved, then every 4 weeks.

CBC, serum ferritin and liver function tests; including serum ALT, serum bilirubin and serum albumin levels and prothrombin activity were measured at each visit, together with abdominal ultrasound examination every month.

The efficacy of therapeutic phlebotomy was evaluated on the basis of biochemical parameters and its safety by the clinical picture and investigations.

RESULTS

Out of 25 patients who have fulfilled the study criteria; those who accepted study protocol were labeled group A (16 patients), those who did not

accept were labeled group B (9 patients) and were used as a control. Three patients of group A were later withdrawn from the study due to non-compliance.

Twelve patients of group A (75%) and 6 patients of group B (66.6%) had serum ferritin levels more than the upper limits of normal at enrollment.

The mean number of phlebotomy sessions needed to induce iron reduction in group A was 9 ± 2 and to maintain it was 4 ± 2 .

Iron depletion therapy significantly reduced serum ALT levels from 83 ± 8 to 42 ± 6 U/L; $P = 0.01$, with normalization of ALT levels in 10/13 (67.9%) of group A at the end of the study period. These changes were not observed in the control group.

Phlebotomy was well tolerated by 16 patients, but 3 patients were withdrawn from the study due to non-compliance. None of the patients developed ascites or other signs of hepatic decompensation as per the Child-Pugh grading system.

The mean baseline data were comparable as follows:-

	Group A (n=16) (Iron Depletion Therapy)	Group B (n=9) (Control Group)	P value
Age (yr)	52.0 ± 3.25	54 ± 2.84	0.72
Male (%)	14 (78.5%)	8 (88.9%)	0.78
Serum ALT (U/L)	75 ± 8	84 ± 5	0.61
Serum albumin (gm %)	3.9 ± 0.14	3.9 ± 0.22	0.68
Hematocrit value (%)	57.6 ± 2.4	58.2 ± 3.1	0.74
Serum ferritin (ng/mL)	264 ± 48	274 ± 39	0.72

DISCUSSION

Hepatic iron overload in patients with CHC has been associated with a more liver pathology^(4,7). Although the exact mechanisms of comorbid pathology are still not clear, the pathogenic role of hepatic iron via the generation of oxidative stress is well established^(23, 24).

The biochemical efficacy and safety of iron reduction/ depletion therapy for patients with CHC has been previously demonstrated⁽¹²⁻¹⁸⁾, the results of the present study suggest the efficacy and safety of iron depletion therapy for patients with HCV-related compensated cirrhosis as well. This is reflected by the achieved significant reduction of serum ALT levels and

normalization of serum ALT levels in 67.9% of the patients who underwent iron depletion therapy, without the development of adverse effects.

Out of the 16 patients included with erythrocytosis included in group A who underwent phlebotomy, only 12/16 (75%) of patients had baseline serum ferritin levels values above the upper limits of normal. Despite the fact that serum iron tests are often used for indirect assessment of iron overload, they frequently lack specificity, with a possible erroneous diagnosis of hepatic iron overload. Several studies have shown no correlation between serum iron levels and hepatic iron stores^(17, 25-29). On the other hand, some studies demonstrated that phlebotomy improves the response to IFN therapy in patients with CHC, irrespective of the liver iron status. It was shown that hepatic iron content in IFN responders was significantly lower than that in IFN non-responders and that the mean of hepatic iron content in the latter group was far below that of iron overload⁽¹⁸⁾. Taken together, these data suggest that the observed beneficial effects of iron depletion therapy in the present study might be also applicable to patients with HCV-related compensated cirrhosis without prerequisite iron overload e.g. the presence of erythrocytosis or increased serum ferritin levels.

In the present study, for the sake of subsequent evaluation of biochemical response to iron depletion therapy, only patients with evidence of elevated serum ALT levels ≥ 1.5 were included. However the beneficial effects of iron depletion might be also applicable to patients with normal/ near normal ALT levels, as it is known that serum aminotransferase levels decrease with the advance of cirrhosis⁽³⁰⁾. High pretreatment serum ALT levels in patients with cirrhosis might not be necessarily an inclusion criterion for iron depletion therapy. In fact, in a recent study to identify the determinants of biochemical response after phlebotomy in patients with CHC infection, multivariate analysis identified ALT < 100 IU/L at the start of phlebotomy as an independent factor associated with ALT normalization⁽³¹⁾.

The results of the present study might recommend further studies for evaluation of effect of iron reduction/depletion therapy for patients with HCV-related compensated cirrhosis as a pre-IFN adjuvant therapy and as a long-term alternative therapy in patients who failed to respond or not candidates for IFN therapy, in order to decrease the incidence of hepatic decompensation and hepatocellular carcinoma, which has been clearly demonstrated in patients with CHC^(12-18, 24).

In conclusion, the results of the present study demonstrate that short term iron depletion by phlebotomy is effective and safe in HCV-related compensated liver cirrhosis with erythrocytosis.

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الملخص العربي

دراسة فعالية وسلامة إنقاص نسبة الحديد علاجيا في المرضى المصابين بالتشمع الكبدى الغير معاوض الناتج

عن فيروس (ج)

يعتبر ترقى إرتفاع نسبة الحديد بالدم والكبد مع الاصابة بالتهاب الكبدى الفيروسى المزمن (ج) من الظواهر المعروفة من أكثر من عشر سنوات. وقد أظهرت الدراسات أن إرتفاع نسبة الحديد بالكبد في هؤلاء المرضى يصاحبه إحداث تغيرات مرضية أكثر في الكبد، بالإضافة إلى ضعف في استجابة هؤلاء المرضى للعلاج بواسطة عقار الانترفيرون، كما أظهرت الدراسات أن إنقاص نسبة الحديد الزائد بواسطة فصد الدم في هؤلاء المرضى يؤدي إلى تحسن وظائف الكبد والتغيرات المرضية بالكبد، مع تحسن استجابتهم للعلاج.

وقد أظهرت الدراسات الحديثة أن وجود ارتفاع بسيط في نسبة الحديد بالكبد قد يكون عاملا مؤثرا يؤدي إلى زيادة التغيرات المرضية بالكبد، كما أن إجراء فصد الدم هؤلاء المرضى أدى إلى حدوث نتائج إيجابية، بصرف النظر عن نسبة الحديد بالكبد قبل العلاج. ومن المعروف علميا أن مرضى التشمع الكبدى يكونون أكثر احتمالا لوجود زيادة في نسبة الحديد بالكبد عن مرضى الالتهاب الكبدى الفيروسى المزمن، إلا أن نتائج فصد الدم في هؤلاء المرضى غير معروفة حتى الآن.

وقد أجريت هذه الدراسة لمعرفة فعالية وسلامة إجراء إنقاص نسبة الحديد علاجيا بواسطة فصد الدم في المرضى المصابين بالتشمع الكبدى الغير معاوض الناتج عن فيروس (ج). وقد أجريت الدراسة على مجموعة من المرضى البالغين المصابين بالتشمع الكبدى الغير معاوض الناتج عن فيروس (ج)، ولديهم إرتفاع في نسبة كرات الدم الحمراء حيث اشتملت على عدد ١٦ مريضا (مجموعة أ) - توقف عن الدراسة ٣ مرضى منهم لعدم انتظامهم في المراجعة في المواعيد المقررة - والذين أجرى لهم فصد للدم بصورة دورية وفقا لاستجابتهم لإنقاص نسبة الحديد بالجسم إلى الحدود المبينة بالدراسة، وتم متابعتهم بالفحوصات اللازمة لمعرفة مدى فعالية هذا الأسلوب العلاجى على تحسن نسبة إنزيم الكبد (ALT)، وكذلك مراقبة حدوث أى تأخر في حالتهم الصحية بالكشف الاكلينيكي والفحوصات اللازمة، ومقارنة تلك الفحوصات بنتائج مجموعة أخرى من المرضى وعددهم ٩ مرضى (مجموعة ب) والذين لم يجرى لهم عملية فصد الدم.

وقد أظهرت النتائج حدوث تحسن ملحوظ في إنزيم الكبد (ALT) في المجموعة (أ) ذو دلالة إحصائية بالإضافة إلى عودة نتائج هذا الفحص إلى الحدود الطبيعية في عدد عشرة مرضى (١٠/١٣ = ٦٧.٩%) عند نهاية فترة الدراسة، وهو ما لم يحدث في مرضى المجموعة (ب)، وذلك بدون حدوث مضاعفات تذكر.

ومن هذه الدراسة يمكن استنتاج أن إنقاص نسبة الحديد علاجيا بواسطة فصد الدم هو إجراء فعال وآمن في تحسن إنزيمات الكبد في المرضى المصابين بالتشمع الكبدى الغير معاوض الناتج عن فيروس (ج) والذين لديهم زيادة في نسبة كرات الدم الحمراء.