Phlebotomy in the Treatment of Iron Overload in Patients with Nonalcoholic and Alcoholic Fatty Liver Diseases

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Abstract

In patients with chronic liver disease, especially nonalcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD) and chronic hepatitis C, iron overload is an important factor for the severity and course of disease. The clinical benefit of phlebotomy as iron reduction therapy in patients with NAFLD and ALD and iron is not clear yet. The aim of our study was to evaluate the effect of phlebotomy in the treatment of patients with NAFLD and ALD and iron overload. Material and methods: A total of 60 patients (45 –male, 15-female; age 44.56±7.19 y.) with serum markers, pointed iron overload (increased levels of serum iron, ferritin and tranferrin saturation > 30%) were included: 30 patients with NAFLD – steatosis (NAS, n= 8) иsteatohepatitis (NASH, n= 22) and 30 patients with ALD – steatosis (AS, n= 10) и alcoholic steatohepatitis (ASH, n= 20) with intakeof alcohol more than 40 g /daily. In patients with NAFLD serum insulin level and HOMA-IR were also assessed. Phlebotomies were carried out periodically according to the standard protocol for a follow-up period of 12 months. Results: In response to phlebotomy, there was a significant decrease (p = 0.001-0.0001) in serum levels of iron, ferritin and transferrin saturation in the whole group of patients, and also in the groups of patients with NAFLD and ALD. An improvement of liver enzymes – AST, ALT and GGT (p = 0.001-0.0001) was also found in the three groups of patients. In patients with NAFLD, a decrease of serum insulin on fasting (basal -18.46 ± 4.32 mIU/L vs11.27 ± 3.54 mIU/L, post phlebotomies, p = 0.005) and HOMA-IR(4.56 ± 2.54 vs 2.68 ± 1.73) were also present. In conclusion, our results show that phlebotomy is a safe and efficient therapy for the patients with nonalcoholic and alcoholic fatty liver disease and iron overload. Regular control of serum iron decrease is essential for the determination of phlebotomies' frequency.

Key words: phlebotomy, iron overload, insulin resistance, nonalcoholic fatty liver disease, alcoholic liver disease

Introduction

Secondary (acquired) iron accumulation in the liver is common in patients with chronic liver disease, especially those with alcoholic etiology, non-alcoholic fatty liver disease and chronic hepatitis C (1,4-7). As with primary haemochromatosis and haemosiderosis the absorption of iron is increased and the ability of the body to increase the excretion is limited. Excess iron leads to cellular damage and directly stimulates fibrogenesis. It is a cofactorfor collagen synthesis. Extraction of excess iron from the body through phlebotomy(blood letting) is the treatment of choice in patients with primary hemochromatosis. The importance of phlebotomy as a method to reduce excess iron accumulated in landfills, and improvement in liver damage in chronic liver disease is still not completely clear.

The aim of our study was to evaluate the effect of phlebotomy in patients with non-alcoholic steatosis and alcohol disease and iron overload.

Material and Methods

The study included 60patients (45 men, 15 women; 44.56 ± 7.19) the serum markers of iron overload (elevated serum iron, ferritin and transferrin saturation above30%): 30 patients with primary non-alcoholic fatty liver disease (NAFLD) - non-alcoholic steatosis (NAS., n = 8) and non-alcoholic steato hepatitis (NASH, (n = 22) and 30 patients with alcoholic fatty liver disease (AFLD, n = 10) and alcoholic steatosis hepatitis (ASH, n =20) with absolute alcohol intake above 40g /L.

Diagnosis of liver disease was brought on the basis of standard criteria and was confirmed histologically. Addition to standardt tests to assess the syndrome of iron overload studied the following parameters: serum iron and serum ferritin. It was estimated and the transferrin saturation. Patients with additional NASD identified serum fasting insulin and HOMA-IR computed as a surrogate marker for insulin resistance.

It was performed therapeutic phlebotomy of 500 ml of blood per week 1 time (maximum 2 times a week) to achieve a mild anemia (hemoglobin up to 110 g / l and hematocrit less than 0.35). Control of hematology and surrogate markers of iron metabolism carried out after losing 1-2 g iron, ie every 4 to 8 weeks for phlebotomy of 500 ml once a week. To ensure the safety of treatment, follow these rules: do not reduce hemoglobin <110 g / l; erythrocytes - <3.8.109 / l; leukocytes - <3.5.109 / l; platelets - <80.109 / l; serum iron - <10 μmol / l for men and <9 μmol / l for women, transferrin saturation - <15%, serum albumin <34 g / l; within limits - they scrutinized before any bleeding. The patients were followed for 12 months.

Static analysis of the results included ANOVA and t-test for paired differences.

Results

Dynamic changes of serum parameters of iron metabolism in tracking studied patients with NAFLD are presented in **Table 1**. We found a significant reduction(p=0.001-0.0001) in serum iron, transferrin saturation and serum ferritinin both the total group of subjects and in different subsets of patients with AFLD and NAFLD. It was decreased and the rate of increasing in the liver enzymes - AST, ALT and GGT (p=0.001-0.0001) also in the whole group and in subgroups of patients with different NASD and ACE(**Table 2**). In addition to these changes in patients with NAFLD was observed a decrease in serum fasting insulin of 18.46 ± 4.32 mIU / L to 11.27 ± 3.54 mIU / L (p = 0.005) and HOMA-IR from4.56 ± 2.54 to2.68 ± 1.73,no further significant changes in serum fasting glucose. Phlebotomy were tolerated well by patients.No serious adversere actions or hypovolaemic effects. 28 of 60t reated patients we reported mild fatigue and dizzinessfor one day after the phlebotomy and in3 patients-mild headaches resolved in the next 2-3days.

Discussion

The high load of iron in the body is not necessarily cause of adisease and shorten the lives of patients, but in the presence of underlying disease, such as non-alcoholic fatty and alcohol disease and chronic hepatitis C can lead to further damage to the hepatic parenchyma and promoting the forming of fibrosis.(1,4, 6, 8, 9). The most reliable and effective treatment for hemochromatosis and secondary overload and the increased deposition of iron blood letting. As a treatment it has been used since ancient times, from the ancient Greek physicians. This method can relatively quickly to reduce total body iron. With the phlebotomy of 500ml of blood is extracted 250 mg iron If there is no anemia, hypoalbuminaemia and ascites, bloodletting is shown and in patients with liver cirrhosis(2).

In our study, we follow standard procedure for the implementation of therapeutic phlebotomy and performing phlebotomy of 500 ml of blood 1 to 2 times a week until a mild anemia. Later the bloodlettig can be reduced to 1 time / month and normally have the value of ferritin - to 4 times / year. This is a maintenance therapy for life (2, 3).

In one year follow-up o fpatients undergoing periodic blood letting, our results show a good correction of the syndrome of iron overload in patients with non-alcoholic fatty liver diease and alcohol disease. Serum iron, transferrin saturation and ferritin were decreased. Similar results were reported by other authors(8,10, 11). In addition to these changes also was shown that in both groups of patients, along with the extraction of excess iron was reduced the activity of serum enzymes AST, ALT and GGT. And other studies have observed a similar improvement in liver enzymes. Our data show that phlebotomy is well tolerated and does not lead to serious side reactions. Blood letting is safe and is associated with transient mild weakness and dizziness. Rarely seen short headache.

Crurical observation is that therapeutic phlebotomy reduces insulin and surrogate marker of insulin resistance HOMA-IR in patients with non-alcoholic fatty disease. Insulin resistance plays an important pathogenic role for steatosis and steatosishepatitis. On the other hand, it is also associated with the development of type 2 diabetes in these patients. It is known that non-alcoholic fatty disease is an independent risk factor for its frequent and earlier onset (5, 10).

L Valenti et al. (2007) and other researchers have also observed a reduction in insulin resistance in non-alcoholic fatty disease or type 2 diabetes. Correction of insulin resistance has an extra-long good effect in patients with non-alcoholic fatty disease not only in the liver but also to reduce the risk of type 2 diabetes and early atherosclerosis.
In conclusion, our results show that phlebotomy is an effective and safe method for the treatment of patients with non-alcoholic steatosis and alcoho ldisease and iron overload. By constantly monitoring the level of reduction of iron in the blood can be adjusted the frequency of blood letting. Properly conducted blood letting is safe and well tolerated by patients.

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Table1. Serum parameters of iron metabolism (x ± SD) in different groups of patients before and after phlebotomy.

	Serum iron (µmol/l)		**Transferrin saturation**(%)		**Serum ferritin** (ng /l)	
	Basic values	After phlebotomy	Basic values	After phlebotomy	Basic values	After phlebotomy
Common group	27,56 ± 9.28	18,49 ± 2.08	39,22 ± 10.32	26,46 ± 8.57	485,68 ±306.29	244,38 ±128.52
NASD	23.48± 5.69	19,53 ± 2.14	35,46 ± 8.57	22,52 ± 7.48	458,32 ±329.44	276,56 ±105.74
ASD	32,24 ± 8.63	22,67 ± 4.28	42,33 ± 8.54	30,26 ± 9.49	528,68 ±234.56	215,34 ±187.32

Table 2. Changes in liver enzyme values(x ± SD) in different groups of patients before and after phlebotomy.

	AST (x URV)		**ALT**(x URV)		**GGT**(x URV)	
	Basic values	After phlebotomy	Basic values	After phlebotomy	Basic values	After phlebotomy
Common group	2,54 ± 1.98	1,54 ± 0,83	3,06 ± 1,57	1,25 ± 1,04	5.28 ± 4.37	2.56 ± 1.57
NASD	2,16 ± 1.78	1,20 ± 1,46	3,25 ± 1,69	1,52 ± 1,86	3.68 ± 1.29	2.02 ± 1.40
ASD	3,46 ± 1.45	1,5 ± 0,78	2,84 ± 1,06	1,44 ± 0,86	8.45 ± 4.24	3.29 ± 1.98

xURV-upper referent value