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Influence of Chronic Hepatitis B and C Infections on Anemia in Hemodialysis Patients

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Abstract

Background

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are frequent among Egyptians hemodialysis patients. Anemia is the most common hematological abnormality in end stage renal disease (ESRD). Long-term effects of HBV and HCV on red blood cell status in ESRD patients are unknown.

Objective

To determine the influence of HBV, HCV, and concurrent HBV and HCV infection on anemia in maintenance hemodialysis patients.

Methods

Retrospective study was performed; one hundred and seven hemodialysis patients were enrolled in the study between Jun 2013 to Mar 2014. According to the results of third-generation enzyme-linked immunosorbent assay and RNA polymerase chain reaction (PCR) the study populations were classified into 44 patients had neither HBV nor HCV (NBC), 22 had HBV positive (HBV), 31 had HCV positive (HCV), and 10 had both HBV/HCV positive (BBC). Differences between the 4 groups of patient variables, including, age, gender, cause of ESRD, duration of hemodialysis, hemoglobin, hematocrit, liver enzymes, iron and ferritin levels, intravenous (IV) Iron dose mg/month and erythropoietin (EPO) dose IU/ month were assessed.

Results

The mean value of hemoglobin (HB) and hematocrit (HCT) of patients with HCV were (11.4±1.3; 33±7.2) respectively, which were significantly higher than the mean value of HB and HCT of NBC (8.8±1.2; 31±5.9), HBV (8.9±1.2; 30±8.8) and BBC (9.0±1.3; 28±1.6) patients (P=0<001; P<0.001) respectively. The IV Iron mg/month and EPO IU/ month doses given to patients with HCV were significantly lesser than the doses given to NBC, HBV and BBC patients (P<0.05; P<0.05) respectively. Although age, gender, duration of hemodialysis, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum iron, serum ferritin, transferrin saturation (TSAT), IV Iron supply and EPO were assessed for association with HB and HCT respectively in HCV group. Only AST, ALT, serum iron, serum ferritin and TSAT were positively correlated with HB and HCT in HCV patients. In the meantime, iron supply and EPO doses, were negatively correlated with HB (P=0. 008; P=0. 001) and HCT (P=0. 05; P=0. 001) respectively.

Conclusion

Hepatitis C infection in hemodialysis patients tends to have higher baseline hemoglobin and decreased need for EPO therapy. However, similar findings were not found in other groups

Keywords: Hepatitis B virus; Hepatitis C virus; Anemia; Hemoglobin; Hemodialysis

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Introduction

Hepatitis B Virus infection is a major global public health problem [1]. Egypt has high endemicity of HBV [2]. Egypt has the highest prevalence of hepatitis C virus in the world, estimated nationally at 14.7% [3.4]. HCV infection and its complications are among the leading public health challenges in Egypt [5].

Hemodialysis procedure per se as well as disturbance in both innate and adaptive immunity make hemodialysis (HD) population susceptible to infection [6,7]. In the past, HBV was the major cause of viral hepatitis in ESRD [8]. However, the introduction of rigorous infection-control strategies and vaccination of susceptible patients and staff led to a decline in the spread of HBV infection in dialysis units [9]. The prevalence of HCV infection in maintenance HD patients substantially increases to up to 90% [10], and this disease has been shown to be associated with severe complications from chronic hepatitis to fatal cirrhosis and hepatocellular carcinoma [11].

Anemia is defined as a reduction in one or more of the major red blood cell measurements; hemoglobin concentration, hematocrit, or red blood cell count. The World Health Organization defines anemia as a hemoglobin level less than 13 g/dL in men and post-menopausal women, and less than 12 g/dL in pre-menopausal women [12]. Anemia is a universal complication among patients with ESRD, due mainly to impaired erythropoietin synthesis by the diseased kidneys, and an absolute or functional iron deficiency [13]. Other contributing factors include inflammation, regular blood loss, hemolysis, vitamin deficiency, hyperparathyroidism and medications [14].

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) anemia guidelines were updated in 2007 to reflect a hemoglobin target range of 11 to 12 g per dL (110 to 120 g per L) in patients with CKD who receive erythropoiesis-stimulating agents [15]. The Anaemia Working Group of European Renal Best Practice (ERBP) suggested a target HB for adults with CKD between 11.0 and 12.0 g/dL, without intentionally exceeding 13.0g/dL [16,17]. FDA labels now warn against erythropoiesis -stimulating agents to achieve hemoglobin levels greater than 11 g per dL because of the risk of death and major cardiovascular events [18].

Patients with HCV tend to have higher ferritin compared with non-HCV patients, as ferritin is an acute phase reactant that is released from the liver with hepatic inflammation [19,20]. Exogenous iron replacement has been known to cause release of free iron and oxyradical formation, which can damage cellular lipids and nucleic acids and, thus, the less iron requirement may be beneficial [21].

Some degree of endogenous EPO production also comes from the liver [22]. The exact site of EPO production in the liver is not clear. Some studies have pointed it out to be located in the Kupffer cells [23], while others believe it to be within hepatocytes surrounding the central veins, along with contributions from the Ito cells in the space of Disse. Hepatonecrosis from inflammation from hepatitis or a regenerating liver post injury could potentially result in the release of EPO from hepatocytes into the circulation [24].

Simple testing for EPO levels to confirm increased hepatic EPO production would be inaccurate in most patients unless they were not receiving any exogenous EPO replacement. In patients receiving exogenous replacement, measurement of their endogenous levels would not be possible because current EPO assays do not differentiate endogenous from exogenous EPO. Normal EPO levels vary from 15 to 19 mIU/mL. However, in response to anemia or hypoxia, these levels can increase 100-fold on an exponential curve. Whether the hepatic production of EPO responds to anemia and hypoxia in a similar fashion to renal EPO production is not known [25].

Long-term effects of HBV and HCV on red blood cell status in ESRD patients are not clear and whether HCV, HBV infections as well as a concurrent HBV and HCV infection are associated with increased red blood cell production. This study was undertaken to assess the effect of HBV, HCV and concurrent HBV and HCV infections on anemia in our hemodialysis population.

Methods

Study Design and Population

Retrospective study was carried out in hemodialys is units of Sharkia governorate which locates in the east of the Egypt-delta, between Jun 2013 to Mar 2014.The study was approved by the local Institutional Ethics Committee.

Demographic information was collected, the total number of the study was107 hemodialysis patients among them 61 males and 46 females (1.3:1), their age ranged from 46-54 year (mean age 50±12.7),on maintenance hemodialysis three times weekly using 3.5 mEq/l dialysate calcium, duration of each dialysis was 4 hours, protocols were not changed during the study with adequate dialysis treatment (Kt/V>1.2),and the main causes of ESRD were chronic glomerulonephritis 32 (29.9%), diabetic nephropathy 27 (25.2%), interstitial nephropathies 16 (14.9%), hypertension 17 (15.8) and unknown 15 (14%).

HBV infection was defined as being positive for hepatitis B virus surface antigen, according to a third-generation enzyme-linked immunosorbent assay (ELISA). HCV infection was defined as being anti–hepatitis C virus antibody positive, according to a third-generation ELISA and confirmed by PCR.

According to the results of third-generation enzyme-linked immunosorbent assay and RNA polymerase chain reaction, the study populations were categorized into 4 groups: Group 1: HBV/HCV negative (NBC), Group 2:HBV positive/HCV negative (HBV), Group 3:HBV negative/HCV positive (HCV), and Group 4:HBV/HCV positive (BBC).

Eligible participants included ESRD on regular hemodialysis (for at least 1 year duration). Participants were excluded from the study if they give a history of blood transfusion, massive blood loss in the last 6 months, polycystic kidney, cryoglobinemia, other causes of liver dysfunction, active malignancy, homeopathic disorder, GIT bleeding and active treatment with interferon or ribavirin.

Laboratory Investigations

All samples were withdrawn from the patients before the hemodialysis session. Anti-HCV antibodies, hepatitis B surface antigen and antibodies were done on a three-month basis. Patient laboratory data, including complete blood picture, hemoglobin (g/dl), haematocrit (%), serum ferritin, serum iron, total iron-binding capacity (TIBC), percent transferrin saturation (TSAT= serum iron x100/TIBC), serum sodium, potassium, uric acid, fasting blood sugar, serum albumin, blood urea nitrogen (BUN), serum creatinine (SCr), AST, ALT, calcium, phosphate, intact parathyroid hormone (i-PTH) were recorded. The average 3-month of HB and HCT and the average 1-month of erythropoietin (EPO) dosage and iron supplement dose were collected for analysis.

Anemia Management Protocol

If the ferritin concentration is < 200 µg/l, IV iron infusion 200–500 mg was given during hemodialysis session. If ferritin >200 g/l and TSAT<20 IV iron infusion, If no response to IV iron and or TSAT >20 start EPO, 4000–6000 IU/wk. Adjust EPO doses by 25%–50% monthly until HB in target range of 11 to 12 g per dL, according to K/DOQI anemia guidelines [15].

Statistical Methods

The parameters of the 4 patient groups were compared using a multivariate general linear model with the Sidak post hoc test. Data are presented as means standard deviations, analysis of variance (ANOVA and LSD tests). Correlation between variables is calculated using the Pearson's and the Spearman correlation tests. Chi square (χ^2) test and the criterion for statistical significance was set at $p< 0.05$. All calculations were carried out using a standard statistical package (SPSS version19).

Results

Demographic Data and Characteristic of Study

The enrolled number of the study 107 participants, their mean age 50 ± 12.7 year, male to female ratio 1.3:1. The 4 patient groups did not differ significantly in age, duration of dialysis, and underlying disease, while the male gender predominates to females.

Demographic data and characteristic of study groups was summarized and shown in Table 1.

Hematological Parameters

The mean value of hemoglobin and hematocrit of HCV patients were 11.4±1.3; 33 ± 7.2 respectively, which were significantly higher than 8.2 1.2; 31 ± 5.9 of NBC patients, 8.9±1.2; 30± 8.8 of HBV and 9.0±1.3; 28 ± 1.6 of BBC. (P< 0.001 and p <0.001) respectively. Without significant difference between the mean value of HB and HCT of HBV, NBC and BBC patients

Table 1: Demographic data and characteristic of the study

		NBC (n =44)	HBV (n = 22)	HCV (n =31)	BBC (n = 10)	P Value
Age (years)		50.2± 14.1	48.0± 9.7	54.0± 12.8	46.0± 10	NS
Sex	Male	20(45.5%)	15(68%)	19(61.3%)	7(70%)	0.05*
	Female	24(54.5%)	7(32%)	12(38%)	3(30%)	
Dialysis duration (months)		57.3 ± 37.4	61.2 ± 32.7	54.8 ± 35.9	52.8 ± 32.6	NS
Causes of ESRD Chronic GN. 32 (29.9%)		12 (26%)	7 (31%)	12 (38.7%)	1(10%)	NS
Diabetic nephropathy 27 (25.2%)		10 (21%)	8 (38%)	8 (25.8%)	1(10%)	NS
Interstitial nephropathies 16 (14.9%)		8 (17%)	2 (9%)	6 (19.3%)	0 (0%)	NS
Hypertension 17 (15.8)		7 (16%)	4 (18%)	4 (12.9%)	2 (20%)	NS
Unknown 15 (14%)		7 (16%)	1(4%)	1(3.3%)	6 (60%)	NS

Values expressed as number of patients (percentage) or mean SD

Biochemical Parameters

HCV infections were also associated with higher levels of RBCs count, AST, ALT, iron, Ferritin and TSAT, (P <0.05, P <0.001, P <0.001, P<0.05, P<0.05 and P<0.05) respectively. HCV patients had a lower platelet count than other groups (P<0.05).

IV Iron and EPO Therapy

The HCV patients required lower doses of IV Iron (mg/month) 105±70 and EPO 8040±8120 IU/ month than other groups (P<0.05; P<0.05) respectively

The mean values of all biochemical characteristics and significant difference between the four groups were available in Table 2.

Correlates of HB and HCT in HCV

Although age, gender, duration of hemodialysis, AST, ALT, serum iron, serum ferritin, TSAT, iron supply and EPO were assessed for association with HB and HCT respectively. Only AST (r=0. 37; P=0. 05) (r=0. 36; P=0. 05), ALT (r=0. 38; P=0. 03) (r=0. 35; P=0. 05), serum iron (r=0. 42; P=0. 01) (r=0. 44; P=0. 01), ferritin (r=0. 36; P=0, 05) (r=0. 40; P=0. 02) and TSAT (r=0. 37; P=0. 05) (r=0. 50; P=0. 006), were positively correlated with HB and HCT in HCV respectively. In the meantime iron supply were negatively correlated with HB and HCT (r= -0.6; P=0. 008) (r= -0.36; P=0. 05) respectively, also EPO doses were negatively correlated with HB and HCT (r= -0.8; P=0. 001) (r= -0.8; P=0. 001) respectively in HCV patients

Table 2: The mean value of all biochemical characteristics of the study

Parameter	NBC (n =46)	HBV (n = 22)	HCV (n =31)	BBC (n = 10)	F	P
Hemoglobin (gm/dl)	8.2 ±1.2	8.9±1.2	11.4±1.3[a, b, d]	9.0±1.3	36.8	<0.001*
Hematocrit (%)	31 ± 5.9	30± 8.8	33 ± 7.2[a, b, d]	28 ± 1.6	11.2	<0.001*
RBCs	3.9±0.62	4.1±0.62	4.2±0.73[a, b, d]	4.0±0.53	2.6	<0.05*
Platelet X10^3/mm^3	300±95	212±71a, d	202±64[a, b, d]	276±46a	11.6	<0.05*
AST (IU/L)	23.1 ± 10.2	31 ± 16.7	38±12.1[a, b, d]	23.1 ± 7.3	16.4	<0.001*
ALT (IU/L)	25 ±11	33 ±16.8	37 ± 11.5[a, b, d]	21.4 ± 10.9	20.5	<0.001*
Albumin (gm/L)	4.4 ± 0.92	4.3 ± 0.7	4.6 ± 0.9	4.4 ± 6.8	0.52	0.67
Intact PTH (pg/ml)	127 ± 131	160± 317	222 ± 510	276 ± 391	0.6	0.5
Serum Iron (ng/ml)	111 ± 75	110 ± 85	158 ± 84[a, b, d]	121 ±63	2.6	<0.05*
Serum Ferritin (ng/ml)	444±385	415± 372	695 ± 479[a, b, d]	411 ± 614	2.7	<0.05*
TSAT (%) TS	40 ± 54	33 ± 71	71 ± 41[a, b, d]	43 ± 8	2.9	<0.05*
TIBC	442±202	392±221	519±169	525±131	2.4	0.07
IV Iron dose (mg/ month)	165±112	156 ±79	105±70[a, b, d]	150±88	2.7 <0.05*	<0.05*
EPO (IU/ month)	13920±9745	12240 ±8288	8040± 8120[a, b, d]	10900±9950	2.7	<0.05*

*P <0.05 in Sidak post hoc test between patients with HCV and NBC, BBC and NBC. a indicates a significant difference as compared to NBC b indicates a significant difference as compared to HBV c indicates a significant difference as compared to BBC

Discussion

Patients with ESRD on maintenance hemodialysis are usually anemic due to lack of EPO secretion from the kidney. However, we observed a few patients in our hemodialysis units with HCV who had a minimal requirement for EPO. So we conduct this study to assess not only the effect of HCV, but also HBV and concurrent HBV and HCV infections on anemia in the hemodialysis population in our units.

In the present study, we demonstrated that hemodialysis patients with HCV infection tended to have higher mean hemoglobin, hematocrit levels and higher levels of RBCs count than other groups. These results are generally compatible with other studies [26-29]. Those observed patients with HCV infection were found to have higher hemoglobin and hematocrit levels compared with HCV-negative and HBV patients. Surprisingly, we observed comparable HB and HCT levels in HBV, NBC and BBC groups. These results are generally compatible with the finding observed by Chih-Bin Chen et al. [28] study, which found hepatitis B virus infection was not associated with increased hemoglobin or hematocrit levels.

The exact mechanisms underlying higher HB and HCT in HCV patients group only are incompletely understood, whoever our findings may reflect increased endogenous erythropoietin production by regenerating hepatocytes [22], an increase of hepatic EPO production was suggested to be related to hepatic regeneration during hepatitis and be proportional to increased interleukin-6 (IL-6) level [30], however previous study observed IL-6 levels were higher in HCV infected patients than in HBV patients [31]. Such observations may explain the higher level HB and HCT among HCV patients than other groups in the current study. Moreover hepcidin exclusively synthesized in the liver, is thought to be a key regulator of iron homeostasis and is induced by inflammation [32]. Relatively low levels of hepatic hepcidin expression of the degree of iron burden may be involved in the pathophysiologic mechanism of increased iron overload in patients with chronic hepatitis C [33,34]. Such observation may help to understand the current results of high serum iron, serum ferritin hence HB and HCT in HCV patients. The potential role of hepcidin in the pathophysiologic mechanism of increased iron overload in HCV patients on HD needs further research.

The current results was not in agreement with Sabry et al. study [35], which showed comparable hemoglobin and hematocrit levels between the two groups (HCV positive and HCV negative). This difference may be attributed to different anemia management protocol and different demographic characteristics between the two studies.

In the present study, we observed that hemodialysis patients with HCV infection tended to have lower platelet counts than other groups. A similar observation was obtained by Chih-Bin Chen et al study [28], which observed that patients with HCV infection had a lower platelet count than those with NBC. Thrombocytopenia is a possible hypothesis for the relation between HCV infection and increase red blood cell production as increased thrombopoietin secretion secondary to thrombocytopenia may increase the number of hematopoietic stem cells and progenitor cells [22].

In the current study, we observed that hemodialysis patients with HCV infection tended to have higher levels of AST, ALT than other groups reflecting hepatic injury. In consistence with other studies [35,36], which observed the HCV infected group to have higher levels of AST, ALT levels than the NBC group

The present study also demonstrated that hemodialysis patients with HCV infection tended to have higher levels of iron, ferritin, TSAT, and TIBC than other groups. Matching study results [28], which also observed that HCV infections were, associated with higher levels of iron, Ferritin and TSAT than NBC and HBV patients. Altered iron metabolism [21], and ferritin as an acute phase reactant that is released from the liver with hepatic inflammation [19], may excuse such high levels of iron parameters in HCV infected patients.

In the current study, we observed that hemodialysis patients with HCV infection tended to have a lesser requirement of iron and EPO in comparison to other groups and in spite of lesser doses of iron and EPO they were achieved the target of K/DOQI anemia guidelines [18]. Similarly, Altintepe et al. [37], and other authors [26-28], concluded that HCV positive patients on hemodialysis required less exogenous erythropoietin and iron than HCV negative patients. We hypothesize that the chronic inflammation as a result of HCV infection or the increased production of the regenerating liver cells causes increased circulating EPO causes improved hematocrit in HCV infection.

In pure financial terms, this may appear to translate to cost savings on EPO at the dialysis centers and to avoid the deleterious effect of hemoglobin levels greater than 11 g per dL because of the risk of death and major cardiovascular events [18].

Conclusion

Hepatitis C infection in hemodialysis patients tends to have higher baseline hemoglobin and decreased need for EPO therapy. However, similar findings were not recorded in patients with hepatitis B infection

Conflict of Interest

No conflict of interest has been declared by the authors.

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