Effect of HCV Infection Versus HBV Infection on the Response to Erythropoietin Therapy in The Treatment of Anemia in Prevalent Haemodialysis Patients

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ABSTRACT

Background: Patients with end stage renal disease (ESRD) on dialytic support are usually anemic due to lack of Erythropoietin (EPO) secretion from the kidney. There was a highly significant association of hemoglobin and hematocrit with HCV infection. Patients with HCV infection were associated with higher hemoglobin and hematocrit compared with non-infected patients. **Aim of this work**: was to study the effect of HBV versus HCV infection on the response to erythropoietin therapy in the treatment of anemia in prevalent hemodialysis. **Subjects and methods:** this study was conducted at Damanhour Fever Hospital hemodialysis unit including 60 patients under regular hemodialysis three sessions a weak and this phase extended from October 2015 till april 2016. Results indicated that hemodialysis patients with HCV and hemodialysis patients with HBV infection had higher mean hemoglobin, than negative group but with no significant statistical difference. **Conclusion**: It could be concluded that hemodialysis patients with HCV tend to have higher baseline hemoglobin (with no significant statistical difference) and decreased need for EPO therapy while patients with HBV infection tend to have higher baseline hemoglobin (with no significant statistical difference) and increased need for EPO therapy.

Keyword: Anemia, Erythropoitin , HCV ,HBV , Dialysis.

INTRODUCTION

Anemia is a common clinical problem in patients with chronic kidney disease and is associated with increased morbidity and mortality. Anemia affects 60% to 80% of patients with chronic kidney disease (CKD) and reduces their quality of life. Treatment options are blood transfusion, epoietin alfa and darbepoetin alfa[(1)].

Anemia of CKD is, in most patients, normocytic and normochromic and primarily caused by depressed production of erythropoietin (EPO), oxidative stress and inflammation, erythropoiesis inhibition and reduction in red blood cell survival[(2)].

The other cause of anemia is deficiency of iron. The dialysis patient is in a state of continuous iron loss from gastrointestinal bleeding, blood drawing, and/or, most important with hemodialysis (HD), the dialysis treatment itself [(3)].

HD patients lose an average of 2 g of iron per year. Thus, iron deficiency will develop in virtually all dialysis patients receiving EPO unless supplemental iron therapy is given orally or intravenously [(3)].

It was shown, that the use of recombinant human erythropoietin (rHuEPO) in haemodialysed patients with chronic renal failure (CRF) stimulates erythropoesis [(4)].

The response to erythropoietin (EPO) treatment varies considerably in individual patients on chronic hemodialysis. The EPO resistance index (ERI) has been considered useful to assess the EPO resistance and can be easily calculated in the clinic [(5)]. Virus infections namely hepatitis B (HBV) and C (HCV) [(4)].

Some studies and case reports indicated attenuated anemia in HD patients with HCV infection, and they previously considered this to be related to increased erythropoietin production after hepatic stimulation by chronic infection with hepatitis virus [(6)].

Anti-HCV(+) HD patients had higher serum EPO levels and required less EPO and iron replacement as compared to anti-HCV(-) patients. Because of the changes in iron metabolism, iron treatment should be carefully administered in HD patients with HCV [(7)].

The influence of hepatitis B (HBV) and hepatitis C virus (HCV) infection on blood hemoglobin (Hb) and serum erythropoietin (Epo) and interleukin-6 (IL-6) concentrations was studied in some anemic patients on regular hemodialysis. Serum immunoreactive Epo levels were significantly higher in patients whose Hb values improved after infection than in patients with persisting anemia after infection. Hb levels were maximal at the time of serum alanine aminotransferase normalization. Red cell production increases as a result of elevated

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circulating Epo during hepatic regeneration after HBV or HCV infection [8].

Patients with chronic active hepatitis induced by HBV infection are characterized by increased plasma EPO concentrations [9].

AIM OF THE WORK

The aim of this work was to study the effect of HBV versus HCV infection on the response to erythropoietin therapy in the treatment of anemia in prevalent haemodialysis.

PATIENTS AND METHODS

This study was conducted to assess the relation between anemia and HCV and HBV infection and anemia in hemodialysis population and to identify the possible relation to erythropoietin doses.

This study included 60 hemodialysis (HD) patients selected from Dialysis Unit in Damanhur Fever Hospital divided into three groups A, B, C according to their virology state into HCV positive, HBV positive and negative groups respectively.

Informed consent was taken from all subjects mentioned and ethical committee approval was obtained.

This study was conducted for six months starting from October 2015 till april 2016 and started by measuring the concentration of hemoglobin for all patients. Then erythropoietin therapy was given according to body weight. Follow up of hemoglobin levels every two months was done. This gave clues about anemia improvement in the three different virology states in those patients.

There were inclusion criteria including prevalent haemodialysis patients >18 years old and transferrin saturation>25%. And exclusion criteria including malignancy, pregnancy, child B, C liver disease, autoimmune diseases, diabetes mellitus, chronic infections and inflammations.

All patients were subjected to full history taking with emphasis on virology state on start of HD, thorough clinical examination, routine laboratory investigations including complete blood picture, renal function tests, liver function tests, iron study (iron, TIBC, and ferritin concentrations), CRP, PTH levels, virology state of the patients. Abdominal sonography was done. Follow up of hemoglobin and haematocrite levels in the three different groups. All results were statistically analysed and tabulated.

The study was approved by the Ethics Board of Ain Shams University.

Statistical Analysis:After data collection, data was revised, coded and fed to statistical software IBM SPSS version 21. The given graphs were constructed using Microsoft excel software.

All statistical analysis was done using two tailed tests and alpha error of 0.05.

The Probability (P-Value) statistical analysis were done at level of significance of $P \leq 0.05$.The following statistical tests were used:

A. Shape of distribution for numeric data

Testing the shape of distribution was done using Kolmogorov-Smirnov Test. Most data was normally distributed and some were skewed data.

B. Descriptive Statistics

1.Count and Percentage: Used for describing and summarizing categorical data.

2.Minimum, Maximum, Arithmetic mean, Standard deviation, Median and Interquartile range: They are used as measures of central tendency and dispersion respectively for normally distributed numeric data. The median and Interquartile range were also added as a measure of central tendency for non-normally distributes data.

The study was approved by the Ethics Board of Ain Shams University.

C. Analytical Statistics

1.Categorical Data

I.Pearson`s chi square test: It is non parametric statistic that is used to test for the association (or relationship) between the categories of two independent samples (row and column variables).

II.Monte Carlo exact test: It is alternative for the Pearson's chi square test if there were more than 20% of cells have expected value. Less than 5.

2.Numeric Data

I.F-Test (Analysis of Variance ANOVA): For normally distributed data, comparison between the three studied groups means was analyzed using ANOVA test.

II.Kruskal Wallis Test: It is used for comparison between different groups when data were non-normally distributed (skewed)

III.Multiple Repeated Measures ANOVA.

IV.Pearson s Correlation coefficient: It is used for assessment of the relationship between two numeric variables.

D.Graphical Presentation

Graphs were done for visual presentation using IBM SPSS version 21.

RESULTS

In the present study, hemodialysis patients with HCV and HBV infection had higher mean hemoglobin, than negative group but with no significant statistical differences.

There was significant statistical differences in MCV, MCH and WBC distribution among the three groups. However, there was no significant statistical differences in the majority of CBC profile as HCT, RBC, MCH.C, RDW.CV, RDW.SD and PLT distribution among the three groups.

Table (1): Distribution of hemoglobin levels among studied prevalent hemodialysis patients and Impact of Erythropoietin treatment on their Hemoglobin levels in fthe current successive cycles versus their virology state ***(Damanhour current Fever Hospital, 2015).***

Virology State	HCV		HBV		Control		Total		Test of Significance	P-Value
HGB Repeated Measures	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD		
HGB.0M	8.02	1.085	8.03	1.59	7.64	2.15	7.897	1.65	**F**=0.357	0.701
HGB.2M	8.48	0.97	8.82	1.45	7.97	2.09	8.42	1.58	**F**= 1.47	0.238
HGB.4M	9.06	0.794	9.29	1.36	8.28	2.01	8.88	1.52	**F**=2.57	0.085
HGB.6M	9.54	0.68	9.84	1.35	8.64	1.99	9.34	1.51	**F**= 3.75	**0.029***
Change in HGB (HGB.0M – HGB.6M	1.52	0.45	1.81	0.32	1.00	0.19	1.44	0.47	**F**= 29.41	**0.001***

F-test (Analysis of Variance ANOVA)
P-Value Significance level at ≤ 0.05
P* Significant

There were significant statistical differences in total erythropoietin dose among the three groups. It was lowest in HCV group then in control and was higher in HBV group.

There was no significant statistical difference in TIBC, transferrin, transferrin saturation, PTH, serum iron and ferritin distribution among the three groups, while there was a significant statistical difference in serum ferritin as it was higher in negative group.

There was no significant statistical difference in HGB at 0 month, HGB at 2 months and HGB at 4 months of follow up among the three groups, while there was a significant statistical difference in HGB at 6 months among the three groups. There is a negative, weak and non-significant relationship between the total erythropoietin dose and change in HGB levels after 6 months of treatment in each group according their virology state

Table (2): Shows that there is a negative, week and non-significant relationship between the total erythropoietin dose and change in HGB levels after 6 months of treatment in each group according their virology state, and there is no statistical significant difference in the person's correlation coefficients among the three groups.

Virology State	HCV	HBV	Control
Pearson's correlation	-0.208	-0.046	-0.121
P-value	0.379	0.848	0.612
Z= 0.232 (P˚ Value= 0.89)			

Z and P˚ value: Using the Fisher r-to-z transformation

DISCUSSION

The current study showed that hemodialysis patients with HCV and hemodialysis patients with HBV infection had higher mean hemoglobin (Hb) (8.02 ±1.085) and (8.03 ± 1.59) respectively, than control group (7.64 ± 2.15) but with no significant statistical differences. While HCT had no significant statistical difference among 3 groups.

As regard HCV, and in agreement with the current study [10,11,12].revealed that anti-HCV-positive patients with end-stage renal disease had higher hemoglobin levels than anti-HCV-negative patients while they observed in against of the current results that anti-HCV-positive patients had higher hematocrit levels than anti-HCV-negative patients.

Also[13,14]. found that hemodialysis patients with HCV infection tended to have higher mean hemoglobin and hematocrit levels than those without HCV infection. Although[13]. found the differences in hematocrit to be not statistically significant.

But the current study was not in agreement with [15].who showed comparable hemoglobin levels between the two groups (HCV positive and HCV negative). While[15]. was in agreement with the current study as it was observed that anti HCV positive patients had comparable hematocrit levels between the two groups.

Also[16,7]did not report any significantly differences in hemoglobin or hematocrit levels between HCV-positive and negative hemodialysis patients.

As regard HBV, in disagreement with the current study,[10]. observed comparable Hb levels in HBV, HBV/HCV negative HBV/HCV positive groups which is compatible with [17].

However[17,19].reported that hemoglobin was significantly higher after hepatitis B virus infection in hemodialysis patients.It was suggested that the liver has some potential to produce EPO apart from the kidneys. Thus, stimulation of hepatic EPO production has been considered as an explanation for lessened anemia in HD patients with viral hepatitis [6].In contrast to the current study, [20]. found that there was increased RBC count in HCV-infected patients, and this was in consistence with the result of a study done by [19]. A similar observation was obtained by [17]which observed that patients with HCV infection had a lower platelet count than those with HBV/HCV negative.

The current study showed that there was no significant statistical difference in TIBC, Transferrin, Transferrin Saturation, PTH and Serum Iron Serum Ferritin distribution among the three groups, while there was a significant statistical difference in Serum Ferritin as it was higher in negative group in disagreement with other studies.

[7,11]concluded that anti-HCV positive patients on hemodialysis required less iron than anti-HCV-negative patients.

There was significant statistical difference in total Erythropoietin dose among the three groups it was lowest in HCV group (128.07) then in control (134.16) and was higher in HBV group (157.3).

[7,11,14,17] concluded that HCV positive patients on hemodialysis required less exogenous erythropoietin than HCV negative patients.

[10] observed that hemodialysis patients with HCV infection tended to have a lesser requirement of iron and EPO in comparison to HBV positive and HBV/HCV negative.

HCV-infected patients needed lower erythropoietin and iron doses than HCV non infected patients [20].

In contrast [21]reported a higher EPO requirement in HCV+ patients versus HCV- patients that were attributed to an altered iron metabolism due to chronic infection.

[22]reported that serum EPO may increase after hepatitis B or C infection, resulting in an improvement of red cell status

CONCLUSION

Hemodialysis patients with HCV tend to have higher baseline hemoglobin (with no significant statistical difference) and decreased need for EPO therapy while patients with HBV infection tend to have higher baseline hemoglobin (with no significant statistical difference) and increased need for EPO therapy.

There was no relation between HCV/HBV infection and iron profile except serum ferritin which was found to be higher in negative group.

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