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Original Article

Chronic hepatitis ameliorates anaemia in haemodialysis patients

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SUMMARY:

Background: Study for influence of chronic hepatitis (CH) on anaemia in haemodialysis (HD) patients remains inconclusive. We aim to characterize the red cell status between CH and hepatitis-free groups among the HD population.

Methods: We retrospectively analysed 80 chronic HD patients from Taipei Medical University Hospital with monthly sampled biochemical study between December 2004 and December 2005. Data classified according to the hepatitis-free, chronic hepatitis B and C groups were expressed as mean ± standard deviation. Student's *t*-test and ANOVA were used to determine the mean difference for continuous variables.

Results: Age, Kt/V, systolic or diastolic blood pressure, body mass index, total cholesterol and triglyceride were not different between CH and hepatitis-free groups. HD duration ($P = 0.0002$), aspartate ($P < 0.0001$), alanine aminotransferase ($P < 0.0001$), alkaline phosphatase ($P = 0.04$), haemoglobin ($P = 0.0066$) and haematocrit ($P = 0.002$) were significantly more elevated in the CH group demanding less erythropoietin dose than in the hepatitis-free group.

Conclusion: Our study demonstrated that lessoned anaemia was observed in CH, which demanded less erythropoietin dose.

KEY WORDS: **anaemia, chronic hepatitis, dialysis, erythropoietin.**

Chronic hepatitis (CH) infection is very common among patients undergoing haemodialysis (HD),[1–4] and HD patients are at high risk of infection with such blood-borne viruses.[5] Rigorous diagnosis and management, especially strictly separation, is a major health concern in this population.[5–9]

Some case reports have addressed attenuated anaemia in HD patients with CH, and they previously considered this was related to increased erythropoietin (EPO) production after hepatic stimulation by chronic infection of hepatitis virus.[10–12]

Up to date, it remains awaited to be worked out whether anaemia of CH in HD population would apparently differ from that in hepatitis-free controls.[10,13] To our knowledge, this is the first study in Taiwan to describe in detail the clinical features of viral hepatitis and red cell status (RCS) presented in HD population. We reappraised the erythropoiesis status in CH cohort for further global survey as our main investigation end-points.[14–16]

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MATERIALS AND METHODS

Subjects

We retrospectively studied all 80 chronic HD patients from Taipei Medical University Hospital between December 2004 and December 2005 after excluding patients with active gastrointestinal bleeding, insufficient folate and vitamin B12, chronic heart failure (CHF) with liver congestion, and active liver or biliary disease of variety of aetiology (total 12 patients excluded), because factors above exert possibilities to interfere with either haemoglobin (Hb) or aspartate/alanine transaminase (AST/ALT) level. No alcoholic hepatitis, nonalcoholic steatohepatitis and storage diseases were presented in our study subjects.

Death (10 patients) and elevated aluminium level during the study period were not included. Each individual received monthly sampled liver function test (LFT) and biochemical study during this period. Mean and standard deviation (SD) of these monthly data were

calculated for comparison. No subjects received blood transfusion in the last 3 months preceding the study. Our patients enrolled had neither renal transplantation nor intravenous drug abuse history. Angiotension-converting enzyme inhibitor, angiotension II receptor antagonist, acetazolamide, theophylline and other drugs with potential effect on erythropoiesis were not used in our subjects. Dialysers for our patients were non-reused cellulose diacetate membrane with variable area according to individual body surface area.

Patients with CH were determined by the following data: hepatitis B surface antigen (HBsAg), anti-HBc antibody, hepatitis B virus (HBV)-DNA, anti-hepatitis C virus (anti-HCV) antibody, or HCV-RNA. Patients were classified as chronic hepatitis C (CHC), chronic hepatitis B (CHB), mixed CHC with CHB and hepatitis-free subgroups for detailed evaluation by *t*-test and ANOVA.

Demographic data and protocol

Serum samples were tested for anti-HCV by using third-generation enzyme immunoassay (EIA.3.0, Abbott Laboratories, Chicago, IL, USA). Samples were also tested for HBsAg and anti-HBc antibody by ELISA (Auszyme Monoclonal, Abbott Park, IL, USA). HBV-DNA or HCV-RNA detection was performed by reverse transcriptase nested polymerase chain reaction for all HBsAg-positive, anti-HBc-positive with negative anti-HBsAg, or anti-HCV-positive patients.

Erythropoietin (Recormon-alfa or beta intravenous injection for all subjects, units per month, or units per kg per week) was used with scheduled protocol: 1000 U/week if haematocrit (Hct) ≥ 32%, 1000 U biweekly if 30% ≤ Hct < 32%, 2000 U biweekly if 28% ≤ Hct < 30%, and 2000 U, 1000 U, 2000 U thrice weekly if Hct < 28%. Continuous variables were expressed as mean ± SD. Iron was necessary to be supplied under absolute or functional iron deficiency during study period (our usual iron supplement profile while iron deficiency: 1000 mg of iron sucrose, Felib × 10 doses for successive 10 dialysis sessions if serum ferritin < 200 μg/L and transferrin saturation (TS) < 20%; 800 mg of iron sucrose, Felib for 100 mg/week during dialysis session, total 8 weeks if serum ferritin ≥200 μg/L and TS < 20%).

Age, sex, HD duration (year), Kt/V, systolic or diastolic blood pressure (SBP/DBP, mmHg), body mass index (BMI, kg/m^2), hepatitis prevalence, patient distribution and percentage among groups were collected. Biochemical parameters, including albumin (Alb, g/dL), AST (U/L), ALT (U/L), alkaline phosphatase (Alk-p, U/L), triglyceride (TG, mg/dL), total cholesterol (Chol, mg/dL), serum iron (SI, μg/dL), ferritin (μg/L), transferring iron binding capacity (TIBC, μg/dL), intact parathyroid hormone (iPTH, pg/mL), C-reactive protein (CRP, mg/dL), Hb (g/dL) and Hct (%) were measured by an automatic analyser (Hitachi 747, Tokyo, Japan). And these data were recorded and analysed to compare mean difference.

Statistical analysis

Data are reported as percentage for categorical parameters and as mean ± SD for continuous variables. The relationships between the quantitative variables were tested using Student's *t*-test or ANOVA. All statistics were performed with the computer software of SPSS for Windows 10.0.1 version (SPSS Inc., Chicago, IL, USA). A *P*-value < 0.05 was taken to be statistically significant.

End-points

We aim to show RCS among hepatitis-free or hepatitis-affected HD patients under protocol EPO administration.

RESULTS

Demographic results between CH and hepatitis-free groups (Table 1)

Among the 80 regular HD patients, 30 patients were positive for viral hepatitis markers, HBV-DNA or HCV-RNA, while the other 50 patients were negative.

Chronic hepatitis accounted for 37.5% of prevalence in our HD population. 62.5% ($n = 50$) were hepatitis-free. There were 45 males and 35 females in our population. The male-to-female ratio was 14:16 in the CH group, but 31:19 in the hepatitis-free group. Between CH and hepatitis-free groups, HD duration (6.6 ± 2.51 *vs* 4.04 ± 2.91 years, $P = 0.0002$) and EPO dose (8533 ± 4897 *vs* 13680 ± 5486 units/month, $P = 0.032$; 40.65 ± 20.13 *vs* 64.61 ± 23.33 units/kg per week, $P = 0.049$) were distinct statistically. Age, Kt/V, SBP, DBP and BMI (as Table 1) were similar.

Table 1 Baseline patient characteristics between chronic hepatitis and hepatitis-free groups

	Chronic hepatitis	Hepatitis-free	*P*-value
n	30	50	
%	37.5	62.5	
Sex (male/female)	14/16	31/19	
Mean ± SD			
Age (year)	62.47 ± 12.47	65.24 ± 14.53	0.37
HD duration (year)	6.6 ± 2.51	4.04 ± 2.91	0.0002*
EPO dose (units/month)	8533 ± 4897	13680 ± 5486	0.032*
EPO dose (units/kg/week)	40.65 ± 20.13	64.61 ± 23.33	0.049*
Kt/V	1.27 ± 0.09	1.3 ± 0.15	0.2
SBP (mmHg)	149 ± 27.9	160 ± 19.7	0.074
DBP (mmHg)	90 ± 17.42	94 ± 15.8	0.28
BMI (kg/m^2)	21.5 ± 2.4	22.4 ± 1.8	0.15

*Significant $P < 0.05$. BMI, body mass index; DBP, diastolic blood pressure; EPO, erythropoietin; HD, haemodialysis; SBP, systolic blood pressure; SD, standard deviation.

Biochemical study in the CH group compared with the hepatitis-free group (Table 2)

Albumin, Chol, TG, iPTH, CRP, SI, ferritin, TIBC and TS were not different between the two groups. AST (25.67 ± 12.07 *vs* 13.08 ± 6.27 U/L, $P < 0.0001$), ALT (29.03 ± 19.43 *vs* 12.34 ± 6.04 U/L, $P < 0.0001$), Alk-p (121.1 ± 69.13 *vs* 83.2 ± 39.2 U/L, $P = 0.04$), Hb and Hct levels (10.55 ± 1.43 *vs* 9.71 ± 0.96, $P = 0.0066$) and (32.1 ± 4.13 *vs* 29.2 ± 3, $P = 0.002$) were apparently elevated in the hepatitis-affected group.

Clinical features among CHC, CHB and mixed CHC with CHB groups (Table 3)

In the CH group, 21 patients were CHC, five patients were pure CHB, and another four were positive for both CHB and CHC (CHC: 26.25%; CHB: 6.25%; mixed CHC with CHB: 5%). Male-to-female ratios were comparable between them. ANOVA for means of parameters in each subgroup including age, AST, ALT, Alk-p, Alb, Hb, Hct, Chol and TG were all similar between subgroups.

Table 2 Biochemical study in the chronic hepatitis group compared with the hepatitis-free group

	Chronic hepatitis	Hepatitis-free	*P*-value
AST (U/L)	25.67 ± 12.07	13.08 ± 6.27	<0.0001*
ALT (U/L)	29.03 ± 19.43	12.34 ± 6.04	<0.0001*
Alk-p (U/L)	112.1 ± 69.13	83.2 ± 39.2	0.04*
Alb (g/dL)	3.83 ± 0.33	3.88 ± 0.38	0.54
Hb (g/dL)	10.55 ± 1.43	9.71 ± 0.96	0.0066*
Hct (%)	32.1 ± 4.13	29.2 ± 3	0.002*
SI (μg/dL)	70.56 ± 20.13	80.22 ± 25.21	0.62
Ferritin (μg/L)	298.2 ± 40.1	284.5 ± 44.2	0.59
TIBC (μg/dL)	250.1 ± 36.1	275.8 ± 31.7	0.08
TS (%)	28.4 ± 5.3	29.1 ± 4.3	0.73
CRP (mg/dL)	1.54 ± 0.88	1.23 ± 0.43	0.8
iPTH (pg/mL)	206 ± 98.3	224 ± 75.5	0.69
Chol (mg/dL)	159.8 ± 39.98	177.1 ± 40.95	0.068
TG (mg/dL)	123.73 ± 61.65	141.12 ± 67.01	0.24

*Significant $P < 0.05$. Data are all mean ± standard deviation. To convert g/dL of serum haemoglobin and serum albumin to g/L, multiply by 10; to convert mmol/L of triglycerides to mg/dL, multiply by 89; to convert mmol/L of cholesterol to mg/dL, multiply by 39. Alb, albumin; Alk-p, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; Chol, cholesterol; CRP, C-reactive protein; Hb, haemoglobin; Hct, haematocrit; iPTH, intact parathyroid hormone; SI, serum iron; TG, triglyceride; TIBC, total iron binding capacity; TS, transferrin saturation.

Table 3 ANOVA for groups between CHC, CHB and mixed CHC with CHB

	Chronic hepatitis			
	CHC	CHB	CHC&CHB	*P*-value
n	21	5	4	
%	26.25	6.25	5	
Sex (male/female)	10/11	2/3	2/2	
Mean ± SD				
Age (year)	65.24 ± 12.88	56.4 ± 10.92	55.5 ± 7.55	NS
AST (U/L)	26.95 ± 12.19	25.4 ± 13.83	19.25 ± 9.8	NS
ALT (U/L)	29.52 ± 18.27	31.4 ± 27.43	23.5 ± 19.16	NS
Alk-p (U/L)	122.52 ± 76.87	91 ± 40.53	83.75 ± 45.16	NS
Alb (g/dL)	3.71 ± 0.29	4.14 ± 0.22	4.08 ± 0.3	NS
Hb (g/dL)	10.61 ± 1.57	10.2 ± 1.1	10.63 ± 1.25	NS
Hct (%)	32.48 ± 4.36	30.4 ± 3.65	32.25 ± 3.77	NS
Chol (mg/dL)	154.48 ± 36.21	178 ± 53.1	165 ± 46.55	NS
TG (mg/dL)	131.29 ± 61.26	103 ± 46.04	110 ± 87.8	NS

Alb, albumin; Alk-p, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CHB, chronic hepatitis B; CHC, chronic hepatitis C; Chol, cholesterol; Hb, haemoglobin; Hct, haematocrit; NS, not significant; SD, standard deviation; TG, triglyceride. To convert g/dL of serum haemoglobin and serum albumin to g/L, multiply by 10; to convert mmol/L of triglycerides to mg/dL, multiply by 89; to convert mmol/L of cholesterol to mg/dL, multiply by 39.

DISCUSSION

High prevalent CHC infection was presented in our cohorts (pure CHC: 37.5%; mixed CHC with CHB: 5%). Under similar experiences, the prevalence of CHC among dialysis patients is broadly reviewed: 25–36% in the United States, 2–63% in Europe, and 22–55.5% in Asia. It was well-known that different methods of control, cleaning and disinfection of the HD membranes, machines, instruments, environmental surfaces, and also duration of HD as similar to our data (6.6 ± 2.51 *vs* 4.04 ± 2.91 years, $P = 0.0002$), interfere with prevalences.[1–5]

The vague clinical picture and the fluctuating pattern of symptoms in dialysis patients with hepatitis often make the diagnosis of CH infection difficult or even impossible if based only on clinical conditions. Although, among dialysis patients, liver biochemical tests were formerly considered as a poor indicator of CH infection, and normal ALT levels cannot exclude viral hepatitis because HD patients have depressed serum ALT levels at baseline,[8,9,17–19] an relatively increased serum AST and ALT concentration, even under conventional normal limits, was still discovered among majority of chronic HD patients with CH when compared with hepatitis-free patients, as shown in some recent publications.[6–8] LFT remained one of the initial convenient screening tests checked monthly and regularly for HD subjects with asymptomatic hepatitis. Consequently, serologic testing, either viral markers or polymerase chain reaction for viral copies, is then essential to recognize this infection and activity.

Causes of the reduction in ALT activity in these patients are only partially known, such as a reduction in pyridoxal-5[1]-phosphate, vitamin B12, coenzyme of ALT, suppression of AST and ALT synthesis in hepatocytes and an inhibition of AST and ALT released from the hepatocyte into the bloodstream, as well as the possibility of liver protection by the hepatocyte growth factor, which is higher in patients with chronic renal failure.[9,17,18]

Many unidentified variables to cause lower level of liver enzymes may require further investigation. With a reduction in the cut-off value of ALT to half of that previously established,[6,19,20] as close to our results, more and more evidence was demonstrated that CH activity in HD patients, when corrected for low ASL/ALT, can still differ from that in normal controls. Until the pathogenesis is studied, and it can be clearly clarified, our only practical means of combating CH in end-stage renal disease patients will remain vigorous, regular, monthly screening and monitoring of AST, ALT with subsequent serological confirmation, control of cross-transmission blood and control of a variety of risk factors like blood contamination or transfusion.[21,22] In our contributions of the publication, elevated AST and ALT while up to 25.67 ± 12.07 and 29.03 ± 19.43 U/L, respectively, even under conventional normal limits, should alert clinicians the possibility for hepatitis in HD units, and perform early detection for serological viral status and viral DNA/RNA study.

Moreover, interestingly there were increased Hb levels and decreased EPO demanding dose in CH. Although there have been many previous reports of cases with improvement of RCS after hepatitis infection in patients on maintenance HD,[11,12] the mechanisms underlying this improvement are incompletely understood. In our review for many case reports and small series of non-randomized studies, the liver has been considered to play a part of role. 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 anaemia in HD patients with viral hepatitis. Studies in partly hepatectomized animals have shown that hepatic EPO formation increases above normal levels during regeneration. Later some studies of the anaemia of renal failure have observed an increase in Hb and Hct levels after infection with HBV, HCV or both in HD population or even in anephric patients.[14–16,23–25]

In the recent explanation for the pathogenesis on the molecular level, increase of hepatic EPO production was suggested to be related to hepatic regeneration during hepatitis and be proportional to increased interleukine-6 (IL-6) level.[10,26–28] Therefore, attention has been paid to the effects of immune modulatory cytokines on erythropoiesis. Actually, other researchers have also found several inflammatory cytokines like interleukine-1 (IL-1), interferon (IFN) and tumour necrosis factor (TNF) that are produced on hepatitis virus infection in hepatic cell cultures inhibit, not stimulate, EPO production.[29,30] Balance between IL-6 and IL-1 as well as IFN and TNF still remains further clarified.

At least in some animal experiments to propose the partial role of IL-6, Kupffer cells and endothelial cells were considered the principal source of IL-6 produced in the livers of mice. IL-6 m-RNA expression and the production of IL-6 were reduced drastically by rat Kupffer cells depletion. It was observed that STAT3 activation after liver disease was compatible with elevated IL-6 level. More recent comprehensive work at animal models indicates that the synthesis of IL-6 and the activation of STAT3 within hepatocytes are critical functions of Kupffer cells and stimulation of EPO production.[31–34]

Although the concentration of circulating IL-6 was not investigated in our study, we were reminded from many frontiers that measurement of IL-6 in blood may not necessarily equate with IL-6 bioactivity. IL-6 is unique, as its action is augmented by binding to IL-6 receptors (IL-6R). Future studies may show if the concentrations of the soluble forms of IL-6R and the expression of their membranous forms are altered in hepatitis virus infection and liver regeneration. These preliminary results still demand more evidence supported by further larger series of randomized study.[35,36]

CONCLUSION

Our study demonstrated that CH which was related to longer HD duration prevails in chronic HD patients, especially CHC. Elevated AST and ALT, even under conventional normal limits, should alert clinicians the possibility for hepatitis in HD units with early detection for serological viral status or viral DNA/RNA study. Interestingly, lessoned

anaemia was observed apparently in CH, which demanded less EPO dose.

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