Hepatitis B viral infection in maintenance hemodialysis patients: A three year follow-up

Ya-Li Cao, Shi-Xiang Wang, Zuo-Min Zhu

Ya-Li Cao, Shi-Xiang Wang, Department of Blood Purification, Beijing Chaoyang Hospital, Affiliate of Capital Medical University, Beijing 100020, China

Zuo-Min Zhu, Department of Clinical Laboratory, Beijing Chaoyang Hospital, Affiliate of Capital Medical University, Beijing 100020, China

Correspondence to: Shi-Xiang Wang, Department of Blood Purification, Beijing Chaoyang Hospital, Affiliate of Capital Medical University, Beijing 100020, China. tzg1219@hotmail.com

Telephone: +86-10-85231455

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Abstract

AIM: To observe the prevalence of hepatitis B virus (HBV) infection in maintenance hemodialysis patients.

METHODS: Eighty-eight hemodialysis patients who had been receiving hemodialysis regularly for an average of 39.45 ± 7.57 (range from 36 to 49) mo were enrolled in this study. HBV markers were measured in these patients before hemodialysis and in 100 healthy controls by the chemiluminescent microparticle immunoassay (CMI) method in order to compare the incidence of HBV infection in hemodialysis patients versus normal healthy people. All patients were then divided into two groups: patients positive for HBV markers (i.e. those positive for HBsAg, anti-HBc, HBeAg, anti-HBe, with or without positive anti-HBs) ($n = 33$), and patients negative for HBV markers (including those only positive anti-HBs) ($n = 55$). The following information was obtained for all patients: socio-demographic data, number of blood transfusions and some laboratory investigations. After 39.45 ± 7.57 mo follow-up, HBV markers were measured in these patients by CMI.

RESULTS: The incidence of HBV infection in maintenance hemodialysis patients was 37.5%, which was higher than in controls (9%). In the patients positive for HBV markers, there were 13 patients (39.4%) who had a history of blood transfusion, which was more than the number [12 (21.8%), $P = 0.04$] of patients negative for HBV markers. Eight of the 88 patients negative for HBV markers turned out to be positive, while three of the 33 patients positive for HBV markers turned out to be negative. There was no cirrhosis of the liver or hepatoma occurring in these patients.

CONCLUSION: Maintenance hemodialysis patients

have a higher risk of HBV infection than the average population. The number of blood transfusions is associated with an increased prevalence of HBV. While it is hard for hemodialysis patients to eliminate HBV, the prognosis of patients with positive HBV markers is good.

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Key words: Hepatitis B virus; Infection; Hemodialysis patients; Maintenance; Prevalence

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INTRODUCTION

Hepatitis B virus (HBV) infection remains a serious issue in the dialysis population^[1-5]. Introduction of HBV vaccination, isolation of HBV positive patients, use of dedicated dialysis machines and regular surveillance for HBV infection has dramatically reduced the spread of HBV in this setting^[6-10]. However, the frequency of HBV infection in patients undergoing maintenance dialysis in the industrialized world is low, but not negligible^[11-14]. Persistent HBsAg seropositivity is much higher in less-developed countries^[15-19], especially in China. The prevalence of HBV infection among hemodialysis patients varies between countries and between dialysis units within a single country. The present study was undertaken to investigate the prevalence of HBV infection among maintenance hemodialysis patients.

MATERIALS AND METHODS

Patients

Eighty-eight patients with ESRD on long-term hemodialysis in the center of blood purification of Beijing Chaoyang Hospital were recruited for this study. There were 42 male and 46 female patients. The median age was 55.46 ± 13.78 (range 25-76) years. The primary cause of ESRD was established in these patients: chronic glomerulonephritis in 35 patients (39.8%), diabetic nephropathy in 22 (25%), hypertension nephropathy in 19 (21.5%), glomerulopathy of unknown origin in 4 (4.5%), tubulointerstitial nephritis in 2 (2.3%), polycystic kidney

Table 1 Variations of HBV markers between hemodialysis patients and healthy controls

Hemodialysis patients	Volunteer controls	HBsAg	Anti-HBs	Anti-HBc	HBeAg	Anti-HBe
18	0			+		
15	2		+	+		
7	0		+	+		+
1	0			+		+
2	1	+			+	
0	6	+				

disease in 2 (2.3%), and renal cell carcinoma in 2 (2.3%). All patients had been on dialysis for 39.45 ± 7.57 (range from 36 to 49) mo. Hemodialysis was performed two to three times each week, 4-4.5 h per session, using single-use dialyzers with a membrane surface area of 1.3-1.7 m². Dialysis membranes were made of polysulfone (36.7%), cellulose acetate (25.4%), or polymethyl-metacrylate (37.9%).

The control group was made up of 100 healthy blood donors and hospital staff [52 males and 48 females, with a median age of 47.25 ± 10.10 (range 35-69) years], whose health status was assessed by periodical general check-ups. These were healthy persons without any infectious, hepatic or kidney diseases.

Methods

Before each patient entered into our blood purification unit, HBV markers were measured, including hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (anti-HBs), antibody to hepatitis B core antigen (anti-HBc), hepatitis B e antigen (HBeAg), and antibody to hepatitis B e antigen (anti-HBe). These markers were also measured in healthy controls. There were 33 (37.5%) patients positive for HBV markers, i.e. patients positive for HBsAg, anti-HBc, HBeAg, anti-HBe, with or without positive anti-HBs. We therefore divided all patients into two groups: patients positive for HBV markers ($n = 33$) and patients negative for HBV markers (including those only positive for anti-HBs) ($n = 55$).

Serum HBsAg, anti-HBs, anti-HBc, HBeAg, and anti-HBe were measured with chemiluminescent microparticle immunoassay (CMI) using an ARCHITECT immunoassay analyzer from the Diagnostics Division of Abbott Laboratories (Abbott Park, IL, United States). Biochemistry data were determined using an AU500 autoanalyzer for blood urea nitrogen (BUN), creatinine, serum albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP).

RESULTS

Incidence of HBV in maintenance hemodialysis patients

There were thirty-three patients with positive HBV markers at the beginning of the study. The incidence of HBV in maintenance hemodialysis patients was 37.5%, which was significantly higher than that in healthy controls. Nine controls were positive for HBV markers. The incidence of HBV in controls was 9%. The variation of the two groups is shown in Table 1.

Table 2 Clinical characteristics and relevant laboratory data (mean $\pm$ SD)

	Positive HBV markers group $n = 33$	Negative HBV markers group $n = 55$	P value
Time on HD, months	38.45 ± 9.34	40.55 ± 8.53	0.245
Blood transfusion	13 (39.4%)	12 (21.8%)	0.042
Biochemical data			
BUN, mg/dL	59.53 ± 12.36	56.47 ± 11.43	0.755
Creatinine, mg/dL	59.53 ± 12.36	56.47 ± 11.43	0.755
Serum albumin, g/dL	3.6 ± 0.6	3.7 ± 0.5	0.206
AST, IU/L	26.3 ± 6.9	23.6 ± 7.4	0.052
ALT, IU/L	18.7 ± 8.3	16.5 ± 10.2	0.235
ALP, IU/L	76 ± 15.7	79 ± 13.6	0.072

BUN: Blood urea nitrogen, detected Pre-dialysis; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; HD: Hemodialysis.

Risk factors of HBV infection

The basic clinical characteristics of the patients are shown in Table 2. In the negative HBV marker group, the mean time on hemodialysis was longer than for the positive HBV marker group, but this difference was not statistically significant. The AST, ALT and ALP levels were, as expected, higher in the positive HBV marker group. The levels of BUN, creatinine, and serum albumin were similar in these two groups. In the positive HBV marker group, there were thirteen patients (39.4%) with a history of blood transfusion, more than the negative group [12 patients (21.8%), $P = 0.04$].

Turnover and prognosis of the two groups

There were twenty-eight patients positive for HBV markers at the beginning of the study. Three of these became negative, such that the rate was 5.4% (1.8% per year). There were 60 patients negative for HBV markers at baseline, eight of whom turned out to be positive, for a rate of 12.7% (4.2% per year). 39.45 ± 7.57 mo later, chronic cirrhosis and hepatoma had not occurred in these patients.

DISCUSSION

This work shows a high prevalence of HBV infection (37.5%) in maintenance hemodialysis patients (Table 1). The prevalence of HBV infection in hemodialysis patients was higher than that of normal controls (9%) and the general population (9.09%)^[20]. This may be attributed to China's high endemic state for HBV infection. A potential contributor to this phenomenon is that significant cellular immune disturbances typically occur in hemodialysis patients. Sharing of supplies, instruments, or medications between hemodialysis patients and reuse of dialyzers would in theory increase the spread of HBV between patients. China, a country hyperendemic for HBV infection, has a higher rate of HBV infection than most industrialized nations. That is why the prevalence rate of HBV infection in our hemodialysis patients is higher than previous observations from western countries (0.9%-5.9%)^[11-14] as well as from other developing nations (4%-17%)^[15-19].

In order to study the risk of HBV infection, we examined the time on hemodialysis, the biochemical data and the history of blood transfusions of the two groups of patients. We conclude that there is an association between blood transfusions and the prevalence of HBV infection. However, there was no significant difference between time on hemodialysis and HBV infection. In our research, although AST, ALT and ALP levels were higher in the positive HBV marker group, this difference was not statistically significant. As for hemodialysis patients, Hung *et al*^[21] revised cutoff values for AST (24 IU/L) and ALT (17 IU/L), which had better sensitivities. In the HBV infected group, the mean values of AST (26.3 IU/L) and ALT (18.7 IU/L) exceeded this criteria, which have important clinical implications in providing benefits of earlier detection and possible prevention of chronic hepatic deteriorations^[22].

Because of cellular immune status disturbances, it is hard for hemodialysis patients to eliminate HBV^[23-26]. In this study, three patients turned out to be negative, giving a rate of 5.4% (1.8% per year). As for the patients negative for HBV markers, eight turned out to be positive, with a rate of 12.7% (4.2% per year). HBV-related liver disease in patients on long-term dialysis often appears clinically mild, with only modest elevations in AST and ALT levels. Few studies have addressed the natural history of HBV in the dialysis population. Josselson *et al*^[27] reported no significant differences in death rates, hospitalizations and hospitalized days between HBsAg-positive and -negative patients on maintenance hemodialysis in the US. However, different outcomes were noted in a retrospective study from India^[28]. HBsAg positive patients had a significantly higher mortality rate than negative patients. In our study, the development of cirrhosis, hepatoma and decompensation of liver function is not observed in HBV infected hemodialysis patients. It has been suggested that the hemodialysis procedures lower HBV DNA levels by various mechanisms: the clearance of HBV DNA by the dialysate, the entrapment of HCV DNA particles onto the membrane surface of dialyzers, and the production of cytokines and other substances during hemodialysis sessions. Rampino *et al*^[29] have measured a prolonged and marked production of hepatocyte growth factor (HGF) during hemodialysis sessions, and have suggested a beneficial effect of HGF through hepatocyte proliferation and accelerated liver repair. Badalamenti *et al*^[30] observed that IFN- α levels markedly increase after dialysis using both cellulose and synthetic membranes. This increase in endogenous IFN could contribute to a reduction in viremia in HBsAg patients on maintenance dialysis.

In conclusion, the incidence of HBV in maintenance hemodialysis patients is significantly higher than the average population. The number of blood transfusions is associated with an increased prevalence of HBV. While it is hard for hemodialysis patients to eliminate HBV, the prognosis for patients with positive HBV markers is good.

COMMENTS

Background

Sharing of supplies, instruments, or medications between hemodialysis patients and reuse of dialyzers would in theory increase the spread of HBV between

patients. Persistent HBsAg seropositivity is much higher in China than in other countries. In order to get the exact prevalence rate of hepatitis B virus (HBV) infection in maintenance hemodialysis patients, we investigate a dialysis unit in China.

Research frontiers

We studied eighty-eight hemodialysis patients who had been regularly receiving hemodialysis for an average of 39.45 ± 7.57 mo. We measured those patients' HBV markers before hemodialysis and after 39.45 ± 7.57 mo follow-up. We get the prevalence of HBV infection in maintenance hemodialysis patients.

Innovations and breakthroughs

Firstly, this work shows a high prevalence of HBV infection (37.5%) in maintenance hemodialysis patients. Secondly, it concludes that there is an association between blood transfusions and the prevalence of HBV infection. However, there was no significant difference between time on hemodialysis and HBV infection. Thirdly, the main difference from other related articles is that we find three positive HBV-infected patients turned out to be negative.

Applications

The actual application value: the prevalence of HBV infection in maintenance hemodialysis patients in China. The perspective of future application: the further study for the exact mechanisms as to how the hemodialysis patients eliminate HBV.

Terminology

Maintenance hemodialysis patients: The patients who suffer from end-stage renal disease have to receive regular hemodialysis.

Peer review

The authors have estimated the prevalence of HBV infection in a hemodialysis unit. It is concluded that maintenance hemodialysis patients have a higher risk of HBV infection than the average population. The number of blood transfusions is associated with an increased prevalence of HBV. While it is hard for hemodialysis patients to eliminate HBV, the prognosis of patients with positive HBV markers is good.

REFERENCES

- 1 Reddy GA, Dakshinamurthy KV, Neelaprasad P, Gangadhar T, Lakshmi V. Prevalence of HBV and HCV dual infection in patients on haemodialysis. *Indian J Med Microbiol* 2005; **23**: 41-43
- 2 From the Centers for Disease Control and Prevention. Outbreaks of hepatitis B virus infection among hemodialysis patients—California, Nebraska, and Texas, 1994. *JAMA* 1996; **275**: 1394-1395
- 3 Petrosillo N, Puro V, Ippolito G. Prevalence of human immunodeficiency virus, hepatitis B virus and hepatitis C virus among dialysis patients. The Italian Multicentric Study on Nosocomial and Occupational Risk of Blood-Borne Infections in Dialysis. *Nephron* 1993; **64**: 636-639
- 4 Mazzoni A, Innocenti M, Consaga M. Retrospective study on the prevalence of B and non-A, non-B hepatitis in a dialysis unit: 17-year follow-up. *Nephron* 1992; **61**: 316-317
- 5 Maisonneuve P, Agodoa L, Gellert R, Stewart JH, Bucciante G, Lowenfels AB, Wolfe RA, Jones E, Disney AP, Briggs D, McCredie M, Boyle P. Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. *Lancet* 1999; **354**: 93-99
- 6 Hutin YJ, Goldstein ST, Varma JK, O'Dair JB, Mast EE, Shapiro CN, Alter MJ. An outbreak of hospital-acquired hepatitis B virus infection among patients receiving chronic hemodialysis. *Infect Control Hosp Epidemiol* 1999; **20**: 731-735
- 7 Rossi GP, Cavallin M, Nussdorfer GG, Pessina AC. The endothelin-aldosterone axis and cardiovascular diseases. *J Cardiovasc Pharmacol* 2001; **38** Suppl 2: S49-S52
- 8 Albertoni F, Battilomo A, Di Nardo V, Franco E, Ippolito G, Marinucci G, Perucci CA, Petrosillo N, Sommella L. Evaluation of a region-wide hepatitis B vaccination program in dialysis

- patients: experience in an Italian region. The Latium Hepatitis Prevention Group. *Nephron* 1991; **58**: 180-183
- 9 **Schmilovitz-Weiss H**, Melzer E, Tur-Kaspa R, Ben-Ari Z. Excellent outcome of Lamivudine treatment in patients with chronic renal failure and hepatitis B virus infection. *J Clin Gastroenterol* 2003; **37**: 64-67
 - 10 **Fabrizi F**, Mangano S, Alongi G, Bisegna S, Finazzi S, Lunghi G, Ponticelli C. Influence of hepatitis B virus viremia upon serum aminotransferase activity in dialysis population. *Int J Artif Organs* 2003; **26**: 1048-1055
 - 11 **Mioli VA**, Balestra E, Bibiano L, Carletti P, Della Bella S, Fanciulli E, Gaffi G, Marinelli R, Perilli R, Ricciatti AM. Epidemiology of viral hepatitis in dialysis centers: a national survey. *Nephron* 1992; **61**: 278-283
 - 12 **Oguchi H**, Miyasaka M, Tokunaga S, Hora K, Ichikawa S, Ochi T, Yamada K, Nagasawa M, Kanno Y, Aizawa T. Hepatitis virus infection (HBV and HCV) in eleven Japanese hemodialysis units. *Clin Nephrol* 1992; **38**: 36-43
 - 13 **Tokars JL**, Miller ER, Alter MJ, Arduino MJ. National surveillance of dialysis-associated diseases in the United States, 1997. *Semin Dial* 2000; **13**: 75-85
 - 14 **Burdick RA**, Bragg-Gresham JL, Woods JD, Hedderwick SA, Kurokawa K, Combe C, Saito A, LaBrecque J, Port FK, Young EW. Patterns of hepatitis B prevalence and seroconversion in hemodialysis units from three continents: the DOPPS. *Kidney Int* 2003; **63**: 2222-2229
 - 15 **Jankovic N**, Cala S, Nadinić B, Varlaj-Knobloch V, Pavlović D. Hepatitis C and hepatitis B virus infection in hemodialysis patients and staff: a two year follow-up. *Int J Artif Organs* 1994; **17**: 137-140
 - 16 **Otedo AE**, Mc'Ligeyo SO, Okoth FA, Kayima JK. Seroprevalence of hepatitis B and C in maintenance dialysis in a public hospital in a developing country. *S Afr Med J* 2003; **93**: 380-384
 - 17 **Teles SA**, Martins RM, Vanderborght B, Stuyver L, Gaspar AM, Yoshida CF. Hepatitis B virus: genotypes and subtypes in Brazilian hemodialysis patients. *Artif Organs* 1999; **23**: 1074-1078
 - 18 **Covic A**, Iancu L, Apetrei C, Scripcaru D, Volovat C, Mititiuc I, Covic M. Hepatitis virus infection in haemodialysis patients from Moldavia. *Nephrol Dial Transplant* 1999; **14**: 40-45
 - 19 **Souza KP**, Luz JA, Teles SA, Carneiro MA, Oliveira LA, Gomes AS, Dias MA, Gomes SA, Yoshida CF, Martins RM. Hepatitis B and C in the hemodialysis unit of Tocantins, Brazil: serological and molecular profiles. *Mem Inst Oswaldo Cruz* 2003; **98**: 599-603
 - 20 **Hepatopathy and Infection institute of Chinese Medical Association**. The prevention and cure guide of chronic hepatitis B. *Zhonghua Neike Zazhi* 2006; **2**: 162-170
 - 21 **Hung KY**, Lee KC, Yen CJ, Wu KD, Tsai TJ, Chen WY. Revised cutoff values of serum aminotransferase in detecting viral hepatitis among CAPD patients: experience from Taiwan, an endemic area for hepatitis B. *Nephrol Dial Transplant* 1997; **12**: 180-183
 - 22 **Fabrizi F**, Martin P, Dixit V, Brezina M, Cole MJ, Vinson S, Mousa M, Gitnick G. Biological dynamics of viral load in hemodialysis patients with hepatitis C virus. *Am J Kidney Dis* 2000; **35**: 122-129
 - 23 **Duarte R**, Huraib S, Said R, Abdel-Khadir A, Sullivan S, Chaballout A, Sbeih F, Mughal T. Interferon-alpha facilitates renal transplantation in hemodialysis patients with chronic viral hepatitis. *Am J Kidney Dis* 1995; **25**: 40-45
 - 24 **Fontaine H**, Thiers V, Chrétien Y, Zylberberg H, Poupon RE, Bréchet C, Legendre C, Kreis H, Pol S. HBV genotypic resistance to lamivudine in kidney recipients and hemodialyzed patients. *Transplantation* 2000; **69**: 2090-2094
 - 25 **Wedemeyer H**, Cornberg M, Tegtmeyer B, Frank H, Tillmann HL, Manns MP. Isolated anti-HBV core phenotype in anti-HCV-positive patients is associated with hepatitis C virus replication. *Clin Microbiol Infect* 2004; **10**: 70-72
 - 26 **Froio N**, Nicastrì E, Comandini UV, Cherubini C, Felicioni R, Solmone M, Di Giulio S, Petrosillo N. Contamination by hepatitis B and C viruses in the dialysis setting. *Am J Kidney Dis* 2003; **42**: 546-550
 - 27 **Josselson J**, Kyser BA, Weir MR, Sadler JH. Hepatitis B surface antigenemia in a chronic hemodialysis program: lack of influence on morbidity and mortality. *Am J Kidney Dis* 1987; **9**: 456-461
 - 28 **Jha R**, Kher V, Naik S, Elhence R, Gupta A, Sharma RK. Hepatitis B associated liver disease in dialysis patients: role of vaccination. *J Nephrol* 1993; **6**: 98-103
 - 29 **Jonquière R**, Bierne H, Fiedler F, Gounon P, Cossart P. Interaction between the protein InlB of *Listeria monocytogenes* and lipoteichoic acid: a novel mechanism of protein association at the surface of gram-positive bacteria. *Mol Microbiol* 1999; **34**: 902-914
 - 30 **Badalamenti S**, Catania A, Lunghi G, Covini G, Bredi E, Brancaccio D, Salvadori M, Como G, Ponticelli C, Graziani G. Changes in viremia and circulating interferon-alpha during hemodialysis in hepatitis C virus-positive patients: only coincidental phenomena? *Am J Kidney Dis* 2003; **42**: 143-150

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