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

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INTRODUCTION
Hepatitis B virus (HBV) infection remains a serious issue in the dialysis population\cite{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\cite{6-10}. However, the frequency of HBV infection in patients undergoing maintenance dialysis in the industrialized world is low, but not negligible\cite{11-14}. Persistent HBsAg seropositivity is much higher in less-developed countries\cite{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...
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.

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

**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. Shifting 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%)[13-14], as well as from other developing nations (4%-17%)[15-19].

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

| Hemodialysis patients | Positive HBV markers group | Negative HBV markers group |
|-----------------------|----------------------------|----------------------------|
| Anti-HBs              | 38.45 ± 9.34              | 59.53 ± 12.36              |
| Anti-HBc              | 59.53 ± 12.36              | 59.53 ± 12.36              |
| HBeAg                 | 40.55 ± 8.53              | 56.47 ± 11.43              |
| Anti-HBe              | 26.3 ± 6.9                | 79 ± 13.6                  |

**Table 2** Clinical characteristics and relevant laboratory data

| Biochemical data | Positive HBV markers group | Negative HBV markers group | P value |
|------------------|---------------------------|---------------------------|---------|
| BUN, mg/dL       | 59.53 ± 12.36             | 56.47 ± 11.43             | 0.075   |
| Creatinine, mg/dL| 59.53 ± 12.36             | 56.47 ± 11.43             | 0.075   |
| 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 ± 13.7                 | 79 ± 13.6                 | 0.072   |

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

Because of cellular immune status disturbances, it is hard for hemodialysis patients to eliminate HBV. 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. 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. 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 dialyser, 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. 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. observed that IFN-alpha 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.

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