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Comparison of hepatitis B surface antibody decay rates after vaccination between hemodialysis and peritoneal dialysis patients

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Abstract

Background and objectives: The available information about maintaining effective immunity after hepatitis B virus (HBV) vaccination in dialysis patients is limited. The aim of this study was to determine whether a difference exists in the persistence of immunity between hemodialysis (HD) and peritoneal dialysis (PD) patients. We compared the decay rate of hepatitis B surface antibody (anti-HBs) titers after HBV vaccination between HD and PD patients.

Design, setting, participants, and measures: A total of 103 HD and 53 PD patients who were completely vaccinated were enrolled. We examined their anti-HBs titers at the 1st month after vaccination then annually thereafter. Changes in the anti-HBs titers were assessed by comparing annual geometric mean titers (GMTs).

Results: The slopes of the anti-HBs titer decay rates plotted on a logarithmic scale for the HD and PD groups were –23.41 and –31.48, respectively. The decay rate of the PD group was significantly faster than that of the HD group (P<0.0053).

Conclusion: The decay rate of anti-HBs titers in the PD group was faster than that in the HD group. Hepatitis B vaccination could not offer long-term protection in HD or PD patients. Post-vaccination testing every 6–12 months is necessary and revaccination may be protective in dialysis patients, especially in hyper-endemic areas of hepatitis B infection.

1. Introduction

Hepatitis B virus (HBV) infection, the leading cause of cirrhosis and hepatocellular carcinoma, is a global health concern [1]. It is important and protective to recommend that dialysis patients receive hepatitis B vaccination and then undergo regular check-ups for hepatitis B surface antibody (anti-HBs) titers [2]. Compared with healthy individuals, dialysis patients show a unique immune response to HBV vaccination. Among the general population, 90–100% of vaccinated subjects acquire protective immunity and maintain protection against HBV 10–15 years later, even after vaccination in infancy [3]. Despite adopting a higher frequency immunization schedule and higher vaccine doses, the vaccination failure rate remains up to 30–60% among dialysis patients [4].

Increasing age, malnutrition, and depression are currently recognized as negative determinants of immune response among the dialysis population [5–8]. In our previous study, we demonstrated that dialysis modality has no effect on response to HBV vaccination [9]. In addition, we observed rapidly declining proportions of seroconversion in hemodialysis (HD) as well as peritoneal dialysis (PD) patients at 2-year follow up. While the unfavorable initial effect of the HBV vaccine in the dialysis groups is documented, few studies have determined the kinetics of the anti-HBs titer waning pattern and the factors affecting immune persistence in the dialysis populations. We aimed to study trends in the decay rates of anti-HBs titers in the dialysis population and compare the decay rates between PD and HD groups. We also attempted to plan an efficient screening and boosting schedule based on the observed trends.

2. Methods

We initiated data collection on dialysis patients at our dialysis center from March 2002 to March 2008, and followed-up these patients until March 2009. We enrolled dialysis subjects who tested negative for HBV surface antigen (HBs Ag) and HBV...
surface antibody (anti-HBs). We excluded patients who were receiving immunosuppressive agents, had malignancies, had previous HBV vaccination, or those who were unable to complete all 4 vaccinations. All patients were vaccinated with a 40 μg recommended hepatitis B vaccine (Engerix-B, GlaxoSmithKline Biologicals) injected into the deltoid muscle at 0, 1, 2, and 6 months.

Initially, there were 124 HD patients and 57 PD patients assessed. We excluded patients who were receiving immunosuppressive agents (1 HD case of frequent acute exacerbation of chronic obstructive lung disease), had malignancies (1 HD case of lung cancer), had previous HBV vaccination (10 HD cases and 2 PD cases, respectively), or those who were unable to complete all 4 vaccinations (9 HD cases and 2 PD cases, who transferred to other dialysis units) (Fig. 1). A total of 156 patients (64 male and 92 female) were enrolled. Serial blood samples were obtained from each available subject at the first month after the final vaccination (time $t_0$), the first year (time $t_1$), and second year (time $t_2$) after the final vaccination, and annually thereafter (time $t_3$, $t_4$, $t_5$). Anti-HBs titers were checked with an ELISA kit (AUSAB-EIA, Abbot Labs, USA). A total of 156 subjects were enrolled; 156 $t_0$ samples, 121 $t_1$ samples, 91 $t_2$ samples, 64 $t_3$ samples, 42 $t_4$ samples, and 13 $t_5$ samples were obtained from these patients. Anti-HBs titers < 10 mIU/ml were regarded as protective in both HD and PD patients. The lower and upper limits of detection using this quantitative method were 0.1 mIU/ml and 1000 mIU/ml, respectively. In the case of undetectable titers, values of 0.05 mIU/ml and 1000 mIU/ml were assigned.

We calculated the geometric mean titers (GMTs) of anti-HBs from the available patients to determine the central tendency of the anti-HBs titers given the skewed distribution of the anti-HBs levels. We traced the trends in the decay rates of anti-HBs titers among the dialysis subjects. We also compared the decay rates of anti-HBs titers between the HD and PD groups.

### 3. Results

#### 3.1. Patient characteristics and response rate

A total of 156 participants (103 HD and 53 PD individuals) were included in our study. Patient characteristics are summarized in Table 1. The GMT of the 156 vaccines checked at the first month after the final injection, the PD group had a higher anti-HBs GMT than the HD group in the first 2 years (Table 2).

#### 3.2. Anti-HBs GMT during 5-year follow-up

The log anti-HBs level is significantly different over time in both HD and PD groups ($P = 0.0011$ and $P < 0.0001$, respectively). The GMT among both dialysis groups was 43.30 mIU/ml at time $t_0$, 13.9 mIU/ml at time $t_1$, 11.3 mIU/ml at time $t_2$, 5.8 mIU/ml at time $t_3$, 4.2 mIU/ml at time $t_4$, and 0.7 mIU/ml at time $t_5$. During annual follow-up after the final injection, the PD group had a higher anti-HBs GMT than the HD group in the first 2 years (Table 2).

### Table 1: Patient characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HD</th>
<th>PD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>103</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>60.89 ± 11.52</td>
<td>51.74 ± 15.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>45:58</td>
<td>19:34</td>
<td>0.393</td>
</tr>
<tr>
<td>Duration of dialysis</td>
<td>41:25 ± 41.39</td>
<td>35:64 ± 28.0</td>
<td>0.522</td>
</tr>
<tr>
<td>DM</td>
<td>37</td>
<td>13</td>
<td>0.205</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>9.71 ± 1.40</td>
<td>9.19 ± 1.32</td>
<td>0.041</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.50 ± 0.37</td>
<td>3.48 ± 0.40</td>
<td>0.958</td>
</tr>
<tr>
<td>Responders (proportion)</td>
<td>71 (68.63%)</td>
<td>38 (71.69%)</td>
<td>0.854</td>
</tr>
</tbody>
</table>

Note: Data are shown as the number (%) or mean ± S.D. as appropriate. Abbreviation: DM, diabetes mellitus.

Comparisons of categorical data were performed by means of the Chi-square test. Continuous data were compared by the non-parametric Wilcoxon rank-sum test. The annual decay pattern of the log anti-HBs level in both HD and PD patients is assessed using the repeated measures ANOVA with the first-order autoregressive variance-covariance structure. We also examined the association between anti-HBs titers and post-vaccination time lapse. A $P$ value < 0.05 was considered statistically significant. The GMT for the anti-HBs levels was computed by the following model: GMT at time $t_n = GMT$ at time $t_0 + (\beta_0 + \beta_1 \log(time))$, where 10 is the base of the natural logarithmic function and $\beta_1$ is the coefficient of this logarithmic function. We examined the differences between the slopes of the logarithmic functions of the HD and PD groups. To take into account the fact that many factors such as gender, age, albumin, and hematocrit levels might influence immune persistence, we used the regression function “titer at time $t_n = \text{titer at time } t_0 + (\beta_1 \log(time))” to identify the slope for each patient. A multiple linear regression model was then adapted to examine the effects of age, albumin, gender, and malignancy on the slope.

### Table 2: GMTs from 5-year follow-up of hemodialysis and peritoneal dialysis patients.

<table>
<thead>
<tr>
<th>G M T s</th>
<th>1st month</th>
<th>1st year</th>
<th>2nd year</th>
<th>3rd year</th>
<th>4th year</th>
<th>5th year</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD</td>
<td>43.3</td>
<td>13.9</td>
<td>11.3</td>
<td>5.8</td>
<td>4.2</td>
<td>0.7</td>
</tr>
<tr>
<td>PD</td>
<td>55.2</td>
<td>16.7</td>
<td>12.7</td>
<td>3.07</td>
<td>1.5</td>
<td></td>
</tr>
</tbody>
</table>

GMT, geometric mean titers.
HBV vaccination is limited, and is almost solely focused on the HD population [5,10–12]. Pasko et al. and others, have shown that about 18.7–100% of HD patients lose their protective immunity in the 1–3 years after HBV vaccination [5,10–12]. Our results provide further support for these observations among the HD population, but we have additionally noted that PD patients also lack consistent immunity against HBV over the 5-year period following HBV vaccination.

Factors influencing the persistence of immunity against HBV among dialysis patients have been investigated in 2 previous studies [10,11] and our results confirm their findings of no impact of age, hematocrit, or gender on the status of effective immunity against HBV after HBV vaccination.

However, although the above studies did follow up on the effective immune status for at least 2 years, they did not determine factors influencing the dynamics of anti-HBs titer decay. In addition, their data were limited to HD patients, so their results relating to the persistence of immunity are not necessarily relevant for PD patients. We demonstrated that the anti-HBs titer decay rate was significantly faster in the PD group than in the HD group. Thus, dialysis modality might be the major factor affecting anti-HBs titer decay in the dialysis population.

Our findings could imply that PD patients cannot maintain effective immunity after HBV vaccination, that is, effective immunoglobulin G (IgG) levels in serum. Reduced IgG synthesis, peritoneal loss, or increased catabolism should all be considered when explaining rapidly reducing serum IgG levels.

Specialized memory B cells or plasma cells produce IgGs after class switching in lymphoid tissues. This lack of immunological memory, conferring protection from viruses such as HBV, requires synergistic actions among memory B cells, memory T cells, and antigen-antibody complexes [12,13]. Bouts et al. revealed a significant correlation between CD27+ B cell numbers and serum IgG level, implying that low levels of memory B cells contribute to low IgG levels in children with chronic renal failure [14]. In addition to declining levels of memory B cells in dialysis patients, amnesic responses to antigen exposure are also impaired. Peces et al. observed that only 50% of dialysis patients with low anti-HBs titers respond adequately to a booster dose [15]. We suggest that both decreasing memory B cell counts and a poor amnestic response account for the difficulty maintaining protective anti-HBs titers in dialysis patients.

The above hypothesis, although it might elucidate the defective immune memory of dialysis patients, cannot explain the discrepancy in the decay rate between the PD and HD groups. We suggest that rapidly declining anti-HBs titers might result from better middle molecule clearance in PD, considering that none of our HD study subjects received hemodialfiltration. In addition, hypogammaglobulinemia has been demonstrated along with low serum IgG, IgG1, IgG2, and IgG4 levels in PD children, and low serum IgG2 and IgG4 levels in PD adults [16–19]. Clinical findings reported by Barbara et al. revealed similar abnormalities in humoral immunity with regard to active immunization against Hemophilus influenza type b in PD children [20]. Thus, we propose that diminished capacity for immune memory and hypogammaglobulinemia concomitantly contributes to the significantly more rapid decay of anti-HBs titers in PD than in HD patients.

Hypoalbunemia was the 2nd influencing waning immunity against HBV in our study. Albumin, exclusively synthesized in the liver, is utilized as a clinical indicator of protein malnutrition. Although transperitoneal albumin losses are inevitable, PD patients are able to increase albumin synthesis to replace such losses [21]. Thus, malnutrition as well as a reduced albumin synthesis rate, resulting from an original decreased protein intake, inflammatory response, or both, would be the chief cause of hypoalbuminemia in either PD or HD patients [22]. Currently, malnutrition is recognized...
as a major cause of secondary immunodeiciencies, and it adversely affects both innate and adaptive immunity [23]. Fernández et al. reported that malnutrition negatively influenced the response to the hepatitis B virus vaccine among HD patients [24]. In our study, hypoalbuminemia accelerated the decay rate of anti-HBs titers in dialysis patients. The results of Fernández et al. in combination with our data suggest that malnutrition might not only affect the initial response to HBV vaccine, but also impair long-term immune memory in dialysis patients [24]. In an animal model of malnutrition, Tetsuji et al. demonstrated that mice with protein-energy malnutrition had significantly lower anti-HBs titers at the 4- and 6-week follow-ups, decreasing the stimulating capacity of spleen dendritic cells, and decreasing the levels of interferon-γ [25]. Thus, hypoalbuminemia weakened humoral immunity through several aspects of the immune pathways, inducing lack of immune memory after vaccination. In addition to the negative impact of old age and malnutrition on protective immunity after HBV vaccination, depression is closely related to antibody response following HBV vaccine in dialysis patients [8]. In our study, we did not examine the influence of depression or health-related quality of life on the consistency of immunity after HBV vaccination in dialysis patients and further study of these factors would be useful.

We attempted to utilize a logarithmic function to re-evaluate the necessity and period of follow-up after HBV vaccination in dialysis patients. David et al. have shown that 39% of HD-vaccinated patients had lost protective anti-HBs titers (>10 mIU/ml) by 6 months. They suggested that yearly screening may not ensure protection against HBV in dialysis patients [26]. Consistent with their findings, about 60–70% of dialysis patients in our study had lost protective immunity by the 1st year after HBV vaccination. In view of high risk of exposure to HBV, poor amnestic immune response after HBV vaccination, and potential risks of transmitting HBV among dialysis patients, intense and frequent monitoring of anti-HBs titers is protective and necessary [27]. At least 6-monthly checks of anti-HBs titers after HBV vaccination would be appropriate based on the present study.

5. Conclusion

This study revealed that the anti-HBs titer decay rate was significantly faster in the in PD than in the HD group. Thus, dialysis modality and malnutrition are major determinants of anti-HBs titer decay rates. Hepatitis B vaccination could not offer long-term protection to either HD or PD patients. Post-vaccination testing at least every 6 months is thus necessary and revaccination may be protective in dialysis patients, especially in hyper-endemic areas of HBV infection.

References