

The effect of paricalcitol on Hepatitis B immunization in hemodialysis patients

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Abstract

Objective: Hepatitis B virus (HBV) infection has high morbidity and mortality. Therefore vaccination for HBV is crucial, especially for risk groups. In this study, we aimed to determine the effect of paricalcitol on HBV immunization in maintenance hemodialysis (HD) patients.

Methods: Forty-two maintenance HD patients enrolled in the study. Group 1 was control who didn't receive paricalcitol treatment (n:28, control group). Group 2 was paricalcitol treatment group for secondary hyperparathyroidism (n:14, paricalcitol group). Anti-HBs titers were measured with a three-month interval for two times.

Results: The mean age of the patients in Group 1 was 58.50(18-80) years, while of the patients in Group 2 was 46.50 (23-81) years. There was no statistically significant difference between the groups in terms of age and gender ($p = 0.200$, $p = 0.508$, respectively). Baseline anti-HBs titer in the control group was 190.32 IU/L (20.18-1000), and 187.89 IU/L (38.77-1000) in the paricalcitol treated group. After 3 months of follow-up, anti-HBs titers decreased to 114.72 IU/L (13.68-1000) from 190.32 IU/L (20.18-1000) in the control group and to the 175.27 IU/L (14.25-1000) from 187.89 IU/L (38.77-1000) in the paricalcitol group. The decrease in anti-HBs titers was significant in the control group, whereas it was not significant in the paricalcitol group ($P = 0.001$, 0.209 , respectively).

Conclusion: The protective effect of paricalcitol on hepatitis B seroconversion in HD patients was observed. We think that paricalcitol may be used as an adjuvant for hepatitis B seroconversion.

Keywords: Hemodialysis, Hepatitis B, Vaccination, Paricalcitol, Vitamin D

Introduction

HBV infection is an important health care problem for all of the world as it in developing countries (1). There are 248 million chronic infected individuals estimated to be infected with HBV (2). In the globe, nearly 3.6% of the individuals are positive for the hepatitis B surface antigen (HBsAg) (3). HBV infection has high morbidity and mortality (2). For this reason vaccination for HBV is crucial, especially for risk groups, and has been used safely over 35 years (3).

HBV rate is higher in HD patients than in the general population (4). Also, this specific group is prominently sensitive to hepatitis B transmission. Impaired immunity, frequent blood transfusion, and common use of the equipments markedly increase the risk (5). Therefore, HBV vaccination has been proposed to prevent infection in all HD patients susceptible to HBV (6). But, patients suffering from hemodialysis cannot show the desired response to HBV vaccination compared to healthy individuals due to insufficient immune response (7,8). There are several reasons to explain this situation.

Chronic inflammation and malnutrition is one of them and generally result in an impaired immune response, and also seen frequently in maintained hemodialysis patients. The development of an immune response to vaccination is a complex state covering innate and adaptive immune systems both. (9). Several adjuvant strategies have been proposed to accelerate the hepatitis B immunization in hemodialysis patients. Levamisole, GM-CSF, Advax (a polysaccharide adjuvant), Polymethylmethacrylate are such adjuvants used to stimulate the immune response (4). Despite all these efforts, enough response to vaccination has not been acquired. Furthermore, patients tend to lose acquired immune response easily compared to healthy individuals (9).

The 1,25-dihydroxycholecalciferol (1,25(OH)₂ D₃), an active form of vitamin D, has a significant role in the immune response. 1,25(OH)₂ D₃ converted from 25-hydroxycholecalciferol (25(OH)₂ D₃) across the kidney through the action of the 1-hydroxylase enzyme (10).



The impact of vitamin D administration has been shown to increase antigen-specific antibody generation on animals. Also reduces the expression of inflammatory cytokines (11).

In light of this knowledge, we postulated that paricalcitol might affect HBV immunization. For this purpose, we retrospectively evaluated the Anti-HBs titer of patients receiving paricalcitol treatment for hyperparathyroidism on HD patients and examined the impact of paricalcitol on HBV immunization. We also examined the probable relationship with the blood counts.

Materials and methods

Study Design

The study was performed retrospectively at Fırat University Hemodialysis Unit. Ethical approval was taken from the local ethical committee (Date:28.03.2019, Decision no: 33). A total of 90 maintenance hemodialysis patients, 42 subjects who meet the criteria were included in the study. All of the participant's anti-HBs titers were above >10 mIU/mL that was accepted to seroprotective. Anti-HBs titers were measured with a three-month interval for two times and titer slopes examined between groups. Patients who have to vaccinate or rappel were not included in the study either between the two intervals or within 1 month of the first Anti-HBs titers measurement because of confounding factors.

Patients Selection and Data Collection

Patients were divided into two groups. Group 1 consisted of controls who didn't receive either paricalcitol or vitamin D treatment (n:28, control group). Group 2 was comprised of patients who received paricalcitol treatment for secondary hyperparathyroidism (n:14, paricalcitol group). Patients who are ongoing on a vaccination schedule or non-sensitive to the vaccine that was defined as anti-HBs concentration <10 mIU/mL have been excluded from the study. All of the participants were older than 18 years. Patients who have a malignancy or thought to have been malnutrition by clinical or laboratory excluded from the study. Testing blood counts, biochemical parameters such as urea, creatinine, PTH, calcium, phosphorus, CRP, and Anti-HBsAg was examined at 0. and 3.months, retrospectively.

Demographic and laboratory data were obtained from the records. The biochemical data used in the study was measured by the ADVIA 2400 device (manufactured by SIEMENS). ARCHITECT Anti-HBsAg method (ABBOTT Laboratories) was used to measure anti-HBs titer which is the so-called chemiluminescence microparticle immunoassay (CMIA).

Statistical analysis

All analyses performed in this study were obtained using the SPSS software program (Version 20.0). Continuous variables were given as mean \pm standard deviation or median values and intervals, and categorical variables were given as absolute numbers. Wilcoxon test was used to evaluate the anti-HBs titer changes in each group. Differences between the groups were evaluated by Mann-Whitney U or Chi-square test. Values less than $p < 0.05$ were considered statistically significant.

Results

A total of 42 patients (24 female, 18 male) were included in the study. In Group 1, there were 28 patients, 13 of whom were women and 15 of them were men. Group 2 consisted of 14 patients, 5 of whom were women and 9 men. The mean age of the patients in Group 1 was 58.50 ± 18 -80 years, while the mean age of the patients in Group 2 was 46.50 ± 23 -81 years. There was no statistically significant difference between the groups in terms of age and gender ($p = 0.200$, $p = 0.508$, respectively). White blood cell, neutrophil, and platelet counts were significantly lower in the paricalcitol group compared to the control group ($P = 0.048$, 0.020 , 0.009 , respectively), but there were no significant differences in terms of lymphocyte, hemoglobin, and MPV (Mean Platelet Volume) values between the two groups. ($P = 0.800$, 0.650 , 0.186 , respectively). There were no significant differences between the groups in terms of biochemical parameters. The comparison of demographic and blood parameters of the groups is summarized in Table 1. The mean paricalcitol dose given to the paricalcitol group was 14.14 ± 10.29 mcg/ week . PTH levels were significantly higher in both the first and the 3. month measurement in the paricalcitol group than the control ($p < 0.001$, 0.048 , respectively) (Table 2) .

The median anti-HBs titer measured at baseline in the control group was 190.32 IU/L (20.18-1000), and also the Anti-HBs titer measured initially in the paricalcitol group was 187.89 IU/L (38.77-1000). After 3 months of follow-up measured anti-HBs titers decreased to 114.72 IU/L (13.68-1000) from 190.32 IU/L (20.18-1000) in the control group and the 175.27 IU/L (14.25-1000) from 187.89 IU/L (38.77-1000) in the paricalcitol group. Although this decrease in anti-HBs titers was significant in the control group, it was not significant in the paricalcitol group. ($P = 0.001$, 0.209 , respectively). The changes in anti-HBs titers in groups is summarized in Table 3.

Table 1. Demographic and blood parameters of groups (* p<0.05)

	Group 1 (Control Group) (median/min-max)	Group 2 (Paricalcitol Group) (median/min-max)	P Value
Gender (F/ M)	13/15	5/9	0.742
Age (year)	58.50 (18-80)	46.50 (23-81)	0.200
CRP (mg/L)	5.86 (3.13-21.20)	5.01 (3.13-60.00)	0.755
White blood cells (mm ³ /mL)	7.01(3.76-12.90)	6.24 (2.99-9.86)	0.048*
Neutrophils (mm ³ /mL)	4.45 (1.83-7.91)	3.76 (1.79-6.00)	0.020*
Lymphocyte (mm ³ /mL)	1.56(0.43-4.95)	1.70(0.74-2.74)	0.800
Hemoglobin (g/dL)	11.45(7.20-13.80)	11.05 (8.50-14.00)	0.650
Platelets	224.5(132.00-594.00)	171.50 (96.00-327)	0.009*
MPV (fL)	8.70(7.50-11.40)	9.10 (7.20-12.00)	0.186
Urea (mg/dl)	121.50(50-232)	141.00 (66.00-245.00)	0.839
Creatinine (mg/dl)	6.92(4.39-14.70)	8.11 (5.15-16.00)	0.157
Calcium (mg/dl)	8.990(6.05-10.43)	9.08 (8.24-11.55)	0.196
Phosphor (mg/dl)	4.00 (1.40-7.90)	5.25 (3.70-7.30)	0.106
Albumin (g/dl)	4.20 (2.80-5.0)	4.20 (7.70-7.30)	0.494
Uric acid (mg/dl)	5.40 (3.80-8.40)	6.10 (4.40-8.50)	0.112
Bicarbonate (mmol/L)	20.10 (13.80-27.40)	19.90 (15.30-24.50)	0.612

CRP, C-reactive protein; MPV, Mean Platelet Volume

Table 2. Comparison of PTH values of groups (* p<0.05)

	Group 1 (Control Group)	Group 2 (Paricalcitol Group)	P Value
PTH (First Value) (pg/mL)	262.0 (2-482)	650.5 (324-1890)	0.001*
PTH (3.Month Value) (pg/mL)	309.5 (2.5-1443)	630.5 (148-1071)	0.048*

Table 3. Anti-HBs titers of groups (* p<0.05)

	Group 1 (Control Group)	Group 2 (Paricalcitol Group)
Anti-HBs (First titers) (IU/L)	190.32 (20.18-1000)	187.89 (38.77-1000)
Anti-HBs (3.Month titers) (IU/L)	114.72 (13.68-1000)	175.27 (14.25-1000)
P Value	P=0.001*	P=0.209

Discussion

Recent advances in vitamin D biology have increased the interest of researchers and clinicians in this field. Vitamin D has not only the effect on the skeletal system but also has an impact on skeletal muscle, immune system cells, adipocytes, pancreas glands, and non-skeletal tissues been shown (12). 1,25 (OH)₂ D₃ directly affects the function of B and T lymphocytes by modulating the effect of the immune system, and also have an impact on antigen-presenting cells and dendritic cells through a change both the phenotype and function of the cells. The immunomodulatory effect of 1,25 (OH)₂ D₃ is generated by either direct action on nuclear transcription factors such as NF-AT and NF-B, or by VDR in promoter regions of cytokine genes (13). Zitt et al. (14), in their retrospective studies, found that patients with vitamin D levels below <10 ng / mL had worse hepatitis B seroconversion levels in patients with chronic kidney disease than those with higher vitamin D levels. Similar to previous study results, Grzegorzewska et al. (11) reported that 25 (OH)₂ D₃ levels were lower in patients who did not respond to the Hepatitis B vaccine compared to responders, but the differences between in groups were not statistically significant.

In the present study, the paricalcitol group was found to have a better seroconversion response than that the control group.

Uremic environment in chronic kidney disease is associated with increased incidence of malignancy, poor immunization response, and increased frequency of infections. It is widely accepted that uremic patients are immunosuppressive. The reason for this situation is unclear and probably multifactorial (15). Sharon et al. studied the effect of paricalcitol on the immune system cytokines such as IL-6, TNF- α , IL-2, and IFN- γ and did not identify any effect on cytokines with used paricalcitol dose (1 mcg of paricalcitol). They also examined the hepatitis B seroconversion (defined as 10 U / mL titer increase) response rate to Hepatitis B booster dose and did not detect any differences in terms of response to booster dose (6 of 13 patients in paricalcitol; 9 of 13 patients in placebo). In this study, the dose of paricalcitol was kept low, due to the high risk of side effects (10). In our study, there was a significant difference in terms of Hepatitis B seroconversion between both groups. The relevant explain

of this differences may be that we had used too much more dose than used by Sharon et al.

It is known that immunological response to hepatitis B vaccine (HBVax) is decreased in patients with chronic kidney disease. A study, which examined the effect of the hepatitis B vaccine on subtypes of regulatory T (Treg) cells in hemodialysis patients and healthy volunteers were performed. Treg levels were measured immediately before vaccination and on days 3, 7, 10, and 14 after vaccination. Accordingly, the study results showed that a significant difference was not found between the two groups. The authors explain this situation by that the IL-10 levels, which have a Treg suppressor feature, were higher in HD patients than the other group (16). In contrast, Gonzalez-Mateo et al. found that the number of CD4 and CD8 T cells was higher in paricalcitol-treated mice than those not-treated. In the same study peritoneal fibrosis was regressed by paricalcitol treatment (17).

Unlike many other infections, vaccination in HBV infection plays an important role as a protective strategy (4). A study in HD patients, the seroconversion rate of HBV was detected at 84 %. The cause of the high seroconversion rate was explained by that a higher dose was used (40 mcg) instead of the traditional hepatitis B vaccine dose (20 mcg) (5). Various methods have been proposed to enhance the response to HBV immunization in chronic kidney patients. These substances used to increase the effectiveness of the vaccine are called adjuvant. For example, high thymopentin doses and Levamisole are such adjuvants used in clinical practice (4). In their meta-analysis, Fabrizi et al. (18) found that the vaccine response may be enhanced in hemodialysis patients when added GM-CSF as an adjuvant to the HBV vaccine. Similarly to these results, we think that paricalcitol may contribute positively to the hepatitis B vaccine response at the clinically used doses. It is clear that, prospective studies are needed to evaluate the paricalcitol to validity as an adjuvant.

Koeffler et al. (19) treated their 12 patients, who have the myelodysplastic syndrome, with high dose paricalcitol and examined patients for changes in blood counts. At the end of 4.5 months, neutrophil and platelet counts were not significantly different in 11 of 12 patients, but there was a significant increase in platelets in only 1 patient. However, the patient had also simultaneous mucormycosis infection which made it difficult to associate with paricalcitol. On the other hand, In the present study, peripheral blood cells such as white blood cell, neutrophil and platelet counts were observed to be significantly lower in the paricalcitol group compared to the control group. The main difference between the two studies was that in the other study very high doses of the paricalcitol was used compared to the present study.

It is known that parathyroidectomy reverses the immunological disorders of patients with high PTH levels. Those patients are sensitive to infections due to immune dysfunction of a variety of reasons. PTH plays a role in the development of dysfunction in various cells of the immune system (20). High PTH levels may play a role in the pathogenesis of impaired immune response in dialysis

patients. Yasunaga et al. revealed the positive effect of parathyroidectomy on the humoral immune system in patients with secondary hyperparathyroidism (21). As PTH levels were high in the paricalcitol group than control in our study this effect does not seem likely.

Conclusion

In conclusion, we have revealed the effect of paricalcitol on hepatitis B seroconversion in maintenance of HD patients. At hemodialysis, paricalcitol is a commonly used drug in the treatment of secondary hyperparathyroidism. However, side effects such as hypercalcemia and adynamic bone disease are the most encountered side effects limiting the its widely clinical use. To be able to use paricalcitol as an adjuvant for hepatitis B seroconversion, we think that both in vivo and in vitro molecular studies are needed to produce paricalcitol biosimilars that only interact in the immune system.

Conflict of Interest: The authors have no conflicts of interest to declare.

Ethical Approval: Ethical approval was taken from the local ethical committee (Date:28.03.2019, Decision no: 33).

Informed Consent: Informed consent was obtained from all patients

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