The Effect of β-Glucan on the Antibody Response to Hepatitis B Vaccination in Chronic Renal Failure Patients

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Abstract

Background. Despite of different vaccination protocols against hepatitis B virus and co-administration of adjuvant therapies, the rate of seroconvertion is still lower in chronic renal failure (CRF) patients. Due to impaired immune system, CRF patients have a suboptimal response to hepatitis B vaccination and frequent boosters are needed to maintain protection. Since β-glucan extracts from *Saccharomyces cerevisiae* is known as an immune stimulant agent, we wanted to evaluate the effect of β-glucan as an adjuvant to the recombinant hepatitis B vaccine on seroconvertion rate and Anti-HBs titers in CRF patients.

Methods. In this open label controlled study, 55 predialytic CRF patients (documented creatinine clearances were between 15 and 30 ml/min) and 14 hemodialysis patients between 18 and 80 years of age were included. The study population was divided into two groups including β-glucan and control groups. All the patients were vaccinated with a containing 40 µg HBsAg dose recombinant hepatitis B vaccine (Genhevac-B 10 µg/ml, Sanofi Pasteur) at baseline, 1 and 2 months. After baseline vaccination, β-glucan group began to take β-glucan 20mg/day for two months. Anti-HBs titers were measured four months later after last vaccination and patient achieving Anti-HBs titer ≥ 10 IU/L was defined as seroconvertion.

Results. Demographics and clinical characteristics of two groups were similar. In β-glucan group, β-glucan was well tolerated. Anti-HBs titers were similar between β-glucan and control groups [21.0 (1.6-164.3) vs 32.9 (4.5-255.5), P=0.63, respectively] and seroconvertion rate was also similar (65% vs 63% respectively, P=0.85).

Conclusions. The result of this study suggests that addition of β-glucan to hepatitis B vaccination has no beneficial effect on anti HbsAg titers and seroconvertion rate in CRF patients.

Key words. β-glucan, hepatitis B vaccination, renal disease, Running Head**:** β-glucan and HBV vaccination in ESRD

Introduction

Chronic renal failure (CRF) severely influences the immune functions of the host and failure of immune functions becomes apparent when vaccinations are applied to CRF patients, particularly against hepatitis B (1, 2). The active vaccination against hepatitis B became available approximately for 20 years and commonly carried out in CRF patients. Nevertheless, despite of vaccination, protective antibody levels develop in only 60% CRF patients (3, 4). Therefore, hepatitis B virus (HBV) infection remains a problem especially in nearly 40% of non-responders in spite of different vaccination protocols and adjuvant therapies (5-10). The lower rate of CRF patients to produce a protective antibody response after hepatitis B vaccination compared to healthy population has been considered to be of multifactorial origin.

β-glucan is β-1,3-glucan with long β-1,6-glucan branches and extracts from *Saccharomyces cerevisiae* cell wall. It stimulates and enhances specific humoral and cellular responses to challenge by infectious organisms. It is known as an immune stimulant agent and activates macrophages, neutrophils, and monocytes and causes releasing cytokines (11). Thus, it might be thought that β-glucan therapy effects on antigen presenting cell activation and increases the immune response to hepatitis B vaccination in CRF patients. Hence, we aimed to investigate the effect of β-glucan administration, as an adjuvant to hepatitis B vaccination, on antibody response and the rate of seroconvertion in CRF patients in present study.

Patients and methods

Study design and patients

This is an open label controlled study. A total of 69 patients (55 predialytic CRF patients with documented creatinine clearance were between 15 and 30 ml/min and 14 hemodialysis [HD] patients) between the ages of 18 and 80 years were included the study. Clinical and demographic characteristics of the patients were recorded. Positive patients for hepatitis B (HBeAg and anti-HBc), acute inflammatory status, malignancy and decompensated chronic liver disease were excluded. In addition, patients with autoimmune disease and received immuno-suppressants in the last three months were also excluded. These subjects had also never received hepatitis B vaccination. Patients were randomized into two groups, control and β-glucan, by the ratio of 2/1. There were 46 patients in the control group and 23 patients in β-glucan group. The study protocol was approved by the local ethical committee and written informed consent was obtained from all patients. All patients were vaccinated with a double doses recombinant hepatitis B vaccine (Genhevac-B 10 µg/ml, Sanofi Pasteur) containing 40 µg of HBsAg at baseline, 1 and 2 months. In β-glucan group, patients also took β-glucan (Immunex 10 mg tablet, Mustafa Nevzat, Istanbul, Turkey) at doses of two tablets per day during the first two months.

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Vaccination protocol and antibody measurement

Vaccines were administered intramuscular to deltoid muscle and patients were kept under medical supervision for hypersensitivity reactions for half an hour after administration. Anti-HBs titers were measured at sixth month. Anti-HBs ≥ 10 IU/L was defined seroconvertion. Anti-HBs titers were measured by third generation ELISA method (Abboth EXIM) and serum albumin level was measured by spectrophotometric method with biochemical auto-analyzer (Hitachi Modular Analyzer Tokyo Japan) at Suleyman Demirel University Biochemistry Laboratory.

Statistical analysis

Continuous variables with a normal distribution are reported as mean ± SD. Anti-HBs titers are presented as median with 25^{th} and 75^{th} percentiles in parenthesis. Statistically significance was assumed at $P < 0.05$. Chi-square test was used to compare nominal parameters and non-nominal parameters were compared by Mann Whitney-*U* test between the two groups.

Results

Patient characteristics

There were 43 out of 69 males and the mean age was 51.9±16.6 years. The main causes of CRF etiologies were hypertensive glomerulosclerosis and diabetic nephropathy. There were 38 predialytic CRF and 8 HD patients in control group whereas 17 predialytic CRF and 6 HD patients in β-glucan group. Control and β-glucan groups were similar for age, gender and baseline serum albumin level (Table 1). β-glucan was well tolerated in β-glucan group.

Seroconvertion rate and anti-HbsAg titers

There were 44 patients achieving seroconversion (29 in control group and 15 in β-glucan group) and seroconversion rate was similar between the two groups (P=0.85). In addition, there was no significant difference between the control and β-glucan group in terms of anti-HBsAg titer (32.9 (4.5-255.5) vs 21.0 (1.6-164.3) respectively, P=0.63).

Discussion

The main finding of this study is that β-glucan as an adjuvant agent at dose of 20 mg per day for two months did not increase the seroconvertion rate and the Anti-HBs titers to hepatitis B vaccination in CRF patients.

At present, different approaches have been used to overcome the non-responsiveness of CRF patients to hepatitis B vaccine. Various strategies including immune modulating agents have been devised to improve the response rate to HBV vaccination in CRF patients, including co-administration of zinc (5) or immune modulators such as gamma interferon (6), thymopentine, a promotor of T-cell maturation (7), IL-2 (8), and granulocyte macrophage colony-stimulating factor for improving both humoral and cellular immune responses (10). This is the first study investigating the effect of β-glucan as an adjuvant agent on antibody response and seroconvertion rate to hepatitis B vaccination in CRF patients. However, there were limitations of present study, including limited number of patients and the heterogeneous of study population. In addition, it is not obvious whether 20mg/day β-glucan therapy for two months is enough to exert the beneficial effect of β-glucan.

Several authors (3, 4) observed that chronic uremic patients, whether dialysed or not, have an impaired immune response to hepatitis B vaccine. Only 50% to 60% of CRF patients develop sufficient Anti-HBs antibodies after hepatitis B vaccination. Unresponsiveness to the HBV vaccine is considered multifactorial in etiology. Immunodeficiency in the majority of uremic nonresponders to hepatitis B vaccination was found as related to a defect in metabolic monocyte function. *In vitro* studies have shown a reduction in interleukin-2 (IL-2) release by peripheral blood mononuclear cells in CRF. As a consequence, T lymphocytes, after activation by antigen, do not receive the monocyte-derived signal required for sufficient production of the T-cell. As monocytes are crucial for IL-2 production and T-cell proliferation, the metabolic monocyte defect associated with uremia might lead to failure of the monocyte population to support the process of primary T-cell activation. It has been demonstrated that β-glucan has a high affinity for β-glucan receptors of human monocytes and neutrophils and binds competitively to the receptor in a dose-dependent manner (12).

Nevertheless, in present study we found that addition of β-glucan therapy at doses of 20mg/day for two months did not increase seroconvention rate and anti HbsAg antibody titers in CRF patients. Also, this could be associated with the short therapy duration and/or low dosage of β-glucan, because the optimal dosage and the duration of β-glucan therapy are not known in CRF patients for achieving optimal response.

Conclusion

In conclusion, adjuvant β-glucan therapy at doses of 20 mg per day for two months did not increase the seroconversion rate and anti-HBsAg antibody titers to hepatitis B vaccination in patients with CRF. Moreover, the effect of long term and higher dose β-glucan administration as an adjuvant agent should be investigated in further studies.

Table 1. Demographic and clinical characteristics of the patients.

Parameters	Control (*n*=46)	β-glucan (*n*=23)	P
Age (year)	53.7±15.6	48.3±18.3	0.23
Gender (M/F)	30/16	13/10	0.48
Primary renal disease (*n*)			
Diabetes mellitus	17	5	0.20
Hypertension	15	9	0.59
Glomerulonephritis	3	2	1.00
Pyelonephritis	4	3	0.67
Amyloidosis	2	2	0.59
Others	5	2	1.00
Predialytic patient (*n*)	38 (83%)	17 (74%)	0.39
Hemodialysis patient (*n*)	8 (17%)	6 (26%)	0.39
Creatinine clearance (ml/min)	10.6±12.9	14.8±12.7	0.76
Serum BUN (mg/dL)	60.0±33.6	63.6±32.2	0.42
Serum kreatinin (mg/dL)	4.46±2.65	5.76±3.75	0.19
Serum albumin (g/dL)	3.83±0.65	3.93±0.52	0.48
Anti-HBs seropositivity (response rate) patient	29 (63%)	15 (65%)	0.85
Anti-HBs titer (IU/L)	32.9 (4.5-255.5)*	21.0 (1.6-164.3)*	0.63

* Median (25-75 percentile). BUN ; blood urea nitrogen.

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