

## Seroprotection after hepatitis B vaccination in chronic kidney disease patients with modified schedule and dosage

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### Abstract

**Background:** This study was conducted to determine the efficacy of four doses of 40 µg vaccine in chronic kidney disease patients as compared to the three-dose 20 µg vaccine schedule given to the normal healthy population.

**Methodology:** This study included 130 chronic kidney disease patients. Of these 84 were given 20 µg vaccine (52 patients were given three doses at 0, one and two months, and 32 patients were given four doses at 0, one, two and six months) and 46 patients were given 40 µg vaccine (30 patients were given three doses at 0, one and two months and 16 patients were given four doses at 0, one, two and six months). Patient response was assessed by measuring antibodies to hepatitis B surface antigen (anti HBs) one month after receiving the third and fourth doses each.

**Results:** Of the patient who received three doses of 20 µg vaccine, 57.7% showed seroprotection while 68.7% of the patients who received four doses of this vaccine showed seroprotection. In contrast, 60% of the patients who received three doses of 40 µg vaccine had seroprotective antibody titers while 87.5% of the patients receiving four doses of 40 µg vaccine showed seroprotection.

**Conclusions:** Seroprotection after four doses of 40 µg vaccine at 0, one, two, and six months was found to be better and cost effective in chronic kidney disease patients compared to three doses of 20 µg vaccine given to normal healthy individuals with adequate renal function.

**Key words:** chronic kidney disease, hepatitis B vaccine, seroprotection

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### Introduction

Prevalence of chronic kidney disease (CKD) is rising worldwide and the global end stage renal disease (ESRD) patient population continues to grow at an alarming rate. ESRD occurs when kidney function is insufficient to sustain life and renal replacement therapy (RRT) is substituted for native kidney function [1,2]. Patients treated with hemodialysis are at a higher risk of blood-borne viral and other infections, both among themselves as well as between the hemodialysis staff and the patients [3]. The prevalence of HBV in the dialysis population in India is reported to range between 3.4-43%, which is several folds higher than the carrier rate in the general population [4].

Hepatitis B vaccination is recommended for all CKD patients. It has been observed that as the severity of renal disease increases, response to the vaccination against hepatitis B virus decreases [5]. Vaccination is therefore recommended for all pre-end stage renal disease patients before they become dialysis dependent and for peritoneal dialysis patients

because they might require in-centre hemodialysis. Presently, there are three hepatitis B vaccines available in India, namely GeneVac B, ShanVac B and Engerix B. They have comparatively similar seroprotection rates<sup>6</sup>, but the cost of Engerix B is much higher than that of the other two. Despite the availability of excellent vaccines and rigorous vaccination schedules, the problem of poor immune response persists. Different hepatitis B regimens with modern recombinant vaccines have been tried in patients with end stage renal disease but were found disappointing, often eliciting only a poor immune response that too was found short-lived [7-10]. To potentiate the efficacy of hepatitis B vaccine, several adjuvants such as the administration of erythropoietin, GM-CSF (Granulocyte monocyte colony stimulating factor) and interleukin have been tried with varied results. All these adjuvants are quite costly and are not easily available [4].

Modifying the current vaccination schedule by augmenting the dosage and duration of vaccination remains the only viable option available for the

**Table 1.** Relationship between vaccine amount, seroprotection rates, and degree of renal dysfunction among renal replacement therapy patients.

Degree of renal dysfunction	20µg vaccine				40µg vaccine			
	After 3 doses		After 4 doses		After 3 doses		After 4 doses	
	No. of cases	Seroprotection	No. of cases	Seroprotection	No. of cases	Seroprotection	No. of cases	Positive cases
Mild Chronic Kidney Disease	22	20(90.1)	12	12(100)	8	8(100)	4	4(100)
Moderate Chronic Kidney Disease	15	10(66.7)	11	10(90.1)	11	10(90.1)	5	5 (100)
End Stage Renal Disease	15	-	9	-	11	6(54.5)	7	5(71.4)
<b>Total</b>	<b>52</b>	<b>30</b>	<b>32</b>	<b>22</b>	<b>30</b>	<b>24</b>	<b>16</b>	<b>14</b>

\* Figures in parenthesis show percentage

majority of ESRD patients of the developing countries who cannot afford these costly adjuvants. This prospective study was conducted to evaluate the post vaccination seroprotection rate among CKD patients after administration of three and four doses of 20 µg and 40 µg of hepatitis vaccine.

### Materials and methods

The study, which included 130 patients of CKD and 45 healthy controls, was conducted in the Nephrology and Microbiology Department at Jawaharlal Nehru Medical College and Hospital, Aligarh, over a period of three years from December 2005 to December 2008. All the cases of hepatitis B, hepatitis C, patients with known conditions such as cirrhosis, portal hypertension, malignancies, and pregnant women were excluded from the study. The study was approved by the Institutional Ethics Committee (IEC) and written consent was taken from all the patients included in the study. All the patients were subjected to thorough clinical examination and investigations including hemogram, urine analysis, renal function test, and liver function test.

Patients were administered recombinant DNA hepatitis B vaccine (Gene Vac B, Serum Institute of India, Pune) after informed written consent was obtained. They were administered either three or four doses of hepatitis B vaccine intramuscularly at 0, 1, 2 or 0, 1, 2 and 6 months. The healthy controls received only 3 doses of 20µg hepatitis B vaccine at 0, 1 and 6 months. All the patients were critically observed for adverse effects.

Patients selected for the study were divided into following groups: Group I was comprised of 46 patients of mild CKD (Serum Creatinine = 1-3 mg %); Group II was comprised of 42 patients of moderate CKD (Serum Creatinine = 3.1-6 mg %); Group III was comprised of 42 patients of end stage renal disease (Serum Creatinine > 6 mg %); and Group IV was comprised of 45 healthy controls. Patients in all the groups were randomly administered 3 or 4 doses of 20 µg and 40 µg vaccine.

Using all aseptic precautions, 3 ml of blood was collected by venepuncture from each vaccinated patient one month after the third dose. One more sample was collected one month after vaccination from the patients who received the fourth dose of vaccine. Serum was separated and stored at -20°C until tested. Quantitative estimation of antiHBs was done using ELISA test (Smartest Diagnostics, Israel). Seroprotection was considered to be achieved when antibody concentration was ≥ 10m IU/ml [6]. Statistical evaluation was done using SPSS 10.0 software whenever needed (Chicago, USA).

### Results

In our study, patients ranged in age from 10 to 70 years and the mean age was 42.18 (± 12.45) years. Among the patients 65.4% were males and 34.6% were females. The mean S. creatinine level for mild CKD, moderate CKD and ESRD was 2.5 ± 1.1mg%, 4.6 ± 1.5 mg% and 8.4 mg% respectively. Mean duration on dialysis was 5.1 ± 7.5 with most being on multiple hemodialysis (92.3%), followed by those on

**Table 2.** Relationship between vaccine amount, seroprotection rates and degree of renal dysfunction among renal replacement therapy patients.

Degree of renal dysfunction	20µg vaccine				40µg vaccine			
	After 3 doses		After 4 doses		After 3 doses		After 4 doses	
	No. of cases	Seroprotection	No. of cases	Seroprotection	No. of cases	Seroprotection	No. of cases	Positive cases
Mild Chronic Kidney Disease	22	20(90.1)	12	12(100)	8	8(100)	4	4(100)
Moderate Chronic Kidney Disease	15	10(66.7)	11	10(90.1)	11	10(90.1)	5	5 (100)
End Stage Renal Disease	15	-	9	-	11	6(54.5)	7	5(71.4)
<b>Total</b>	<b>52</b>	<b>30(57.7)</b>	<b>32</b>	<b>22(68.7)</b>	<b>30</b>	<b>24(80)</b>	<b>16</b>	<b>14(87.5)</b>

\* Figures in parenthesis shows percentage

CAPD (5.4%) and renal transplant (3.4%). Among the healthy controls 53.3% were males and 46.65 were females .Their mean age was  $38.16 \pm 5.24$  years and the mean S. creatinine level was  $0.3 \pm 0.2$  mg% (Table 1).

All the patients with mild CKD achieved seroprotection when given 40 µg vaccine (three or four doses) or four doses of 20 µg vaccine, while only 90.1% of those given three doses of 20 µg vaccine could be seroprotected. Among the patients with a moderate degree of renal disease, all those given four doses of 40 µg vaccine attained seroprotection; however, the rate of seroprotection decreased to 90.1% when only three doses were given (either 20 µg or 40 µg). Seroprotection rate further declined to 66.7% when only three doses of 20 µg vaccine were administered. None of the patient with ESRD had seroprotective levels of antibodies when 20 µg vaccine (three or four doses) was used, while 54.5% and 71.4% of seroprotection rate could be achieved on administration of three and four doses of 40 µg vaccine respectively (Table 2)

In this study, it was observed that the seroprotection attained after four doses of 40 µg vaccine (87.5%) was significantly higher than three doses of 20 µg vaccine (57.6%;  $p < 0.05$ ).Among healthy controls given three doses of 20 µg vaccine, 93.3% showed seroprotection. Healthy controls attained significantly higher seroprotective rates as compared to chronic kidney disease patients on renal replacement therapy ( $p < 0.05$ ).

### Discussion

Despite the introduction of hepatitis B vaccination as well as the practice of isolating hepatitis B positive patients and the use of modern dialysis machines, control of hepatitis B virus (HBV) infection has been a continuous challenge in the management of patients with advanced kidney disease. HBV infections are still difficult to treat, so the main objective is disease prevention by timely immunization with hepatitis B surface antigen vaccines. In the general population, a simple two- or three-standard-dose vaccination strategy has been proved to be highly successful. In contrast, an intensified and more tailored approach is evolving in patients with advanced renal failure as the seroprotection rates of CKD patients are still poor when compared to those of the normal healthy population [11]. Among them the most worrisome category remains the patients with a severe degree of renal failure.

In this study, hepatitis B post vaccination seroprotection was assessed in patients with varying degrees of renal failure. Of the patients given three doses of 20 µg vaccine, 57.7% attained seroprotective antibody titers. Our results mirror those from previous authors [9,12,13] who also showed similar seroprotection rates. On comparing these patients with those given three doses of 40 µg vaccine, it was seen that a much larger number of patients (80%) could be seroprotected. In our study, 68.7% patients given four doses of 20 µg vaccine achieved seroprotective antibody titers while among those given four doses of 40 µg vaccine, 87.5% of the

patients attained significantly higher seroprotection levels.

It appears that the degree of renal failure was one of the major determinants for the attainment of differential seroprotection rates in renal failure patients. It was observed that patients with mild CKD showed better seroprotection rates as compared to those with moderate CKD, and these in turn were better seroprotected in comparison to those with ESRD. However, when we compared the seroprotection rates in relation to the degree of renal failure and the amount of vaccine administered, it was seen that in all three groups of patients, seroprotection was better when 40 µg of vaccine was used as compared to 20 µg of vaccine. In cases of mild CKD patients, 20 µg of vaccine was almost as good as 40 µg of vaccine, and in all those patients with a moderate degree of chronic kidney disease, a significant difference was seen when 40 µg of vaccine was used as compared to 20 µg of vaccine. The most striking difference in seroprotection rates, however, was seen in patients with a severe degree of chronic kidney disease where none of the patients were seroprotected when either three or four doses of 20 µg vaccine was administered, whereas on giving 40 µg of vaccine, 54.5% and 71.4% seroprotection was detected after three and four doses respectively. No adverse effects whatsoever were observed on doubling the dose of hepatitis B Vaccine. Our study proved to be more cost effective than other studies that used expensive adjuvants such as erythropoietin, GM-CSF, and interleukin, as we observed comparable seroprotection rates [14]. In fact, according to some studies, these adjuvants even failed to increase the seroprotection rates [12,15]. We therefore recommend giving four doses of 40 µg vaccine to chronic kidney disease patients, especially those with moderate to severe degrees of chronic kidney disease. Simply doubling the usual dose of the vaccine and adding one more dose in the schedule provided superior and more cost effective seroprotection in CKD patients, especially for those with moderate to severe degrees of chronic kidney disease.

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**Conflict of interests:** No conflict of interests is declared.