Immunogenicity and Efficacy of Hepatitis B Vaccination in Indian Chronic Renal Failure Patients on Hemodialysis and After Renal Transplantation

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Dear Sir,

The incidence of Hepatitis B virus (HBV) infection is high among hemodialysis (HD) patients. The HBV vaccines in chronic renal failure (CRF) have been shown to stimulate antibody response only in 50-60% of patients [1]. It is not only the immune response to hepatitis B vaccine which is low in HD patients, but also to other antigens like tetanus and diphtheria toxoids [2]. Even among those who respond to these antigens, the response is usually transient. In developing countries like India, where the HBV carrier rate continues to be in the range of 0.9-4% [3], fresh infection within dialysis units is a matter of concern. Since reasons for the low response rate to vaccine among CRF patients is ill understood and has been attributed to uremia [4], it is expected that the defect should get corrected after renal trans-plantation. In this study, we have investigated immune response to HBV vaccine, HBV infection rate among vaccinated CRF patients and the anti-HBs response to booster dose of vaccine in low responders following renal transplantation.

Seventy-one CRF patients (mean age $\pm$ SD 38 ± 12 years) with serum creatinine of 11 ± 2.6 mg/dl, serum urea of 103 ± 48 mg/dl and on regular HD for a period of 6.7 ± 6 months were included in this study. All the patients were negative for hepatitis B surface antigen (HBsAg) prior to the start of HD. Serial monthly samples were collected throughout the course of treatment. This center performs only live related donor transplantations since the harvesting of cadaver organs is still not permitted by law in our state (Uttar Pradesh). Being a public funded hospital in the region where there are few HD machines, the institutional policy is to continue HD only till the patient and the prospective donors are fully investigated for live related transplantation. In the absence of a suitable and willing donor, HD is discontinued at our center, while those with donors are transplanted at the earliest. This policy has been adopted in order to relieve stress on the HD unit and to give maximum benefit to patients. Double the standard dose (40 μ g) of recombinant HBsAg vaccine (En-gerix B) was given intramuscularly in the deltoid region at 0, 1 and 2 months to all CRF patients on HD. An additional booster dose was given to the low responders (median 8 months) after renal transplantation. These patients were on maintenance doses of immunosuppression (cyclosporin A 2-3 mg/kg, prednisolone 0.2

mg/kg and azathioprine 1 mg/kg body weight). The usual practice of a fourth booster dose at 6 months was not possible in these patients nor was it possible to get a control group of nonresponders who were not transplanted because of the hospital policy outlined above. Antibody titer to HBsAg (anti-HBs) was estimated in all patients 4-8 weeks after the third dose of vaccine by a solid-phase quantitative ELISA (Organon Teknika). The protective titer of anti-HBs was defined as $> 10 \text{ IU/l}$. The patients with $> 10 \text{ IU/l}$ were taken as responders (mean age $\pm$ SD 38 ± 13 years) and those with $< 10 \text{ IU/l}$ were nonresponders (mean age $\pm$ SD 38 ± 11 years). Serial monthly samples of all patients were tested for HBsAg status in order to detect possible fresh infections. Statistical analysis was performed using χ test for HBV infection rate among low responders and paired t test for comparison of anti-HBs antibody titers among low responders, before and after transplantation.

All 71 CRF patients who received HBsAg vaccination were negative for HBsAg at onset of dialysis and prior to vaccination. Forty-five (57.8%) developed protective titers of anti-HBs and 26 (42.2%) failed to mount an adequate anti-HBs response. Of the 26 patients who did not mount an adequate anti-HBs response, 5 patients became HBsAg positive during dialysis (6 months) and none among the 45 patients with adequate antibody response became HBsAg positive ($p < 0.01$). Five patients who had low anti-HBs titer were subsequently transplanted with grafts from live related donors, and were revaccinated with one additional dose of 40 μ g Engerix B. These patients had normal renal function in the posttransplant period but were on standard immunosuppressive regimen. The vaccine booster was given to see if the ability to mount anti-HBs response would improve. The booster dose significantly altered the anti-HBs titer in these patients ($p < 0.02$). The mean anti-HBs antibody titer in 5 pretransplant and post-transplant patients were 7 and 50 IU/l respectively. Our results have shown that in Indian patients with CRF on maintenance HD, hepatitis B vaccination resulted in successful seroconversion only in 57.8% of patients. The patients who failed to develop

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protective antibody titer were at higher risk of developing infection during subsequent HD therapy. Studies from other centers have reported a seroconversion rate of 23-33% after 3 doses of vaccine at 0, 1 and 2 months which after the fourth booster dose was 40% [5] and 62% [1]. The seroconversion rate after 3 doses of vaccination in our patient population of 58% was higher than in these reports. Neither the age nor the duration of HD seem to correlate with the seroconversion rate. There is no doubt that the institution of a regular vaccination programme brings down the frequency of HBV infection. It dropped from 3 to 0.2% in the USA [7] and from 32 to 4.7% in our center [8]. However, it is clear from our prospective follow-up data that these patients are still at a higher risk of developing fresh infections, since the incidence of 5/71 (7.04%) is far higher than the population incidence of 0.9-2.2% [3, 6]. Among the measures that have been tried to decrease fresh HBV infection in the dialysis population was administration of an additional dose of vaccine along with recombinant interleukin (IL)-2 as a supplement [9, 10]. This approach substantially increased the responder rate but is an unrealistic option for a country like India due to the cost factor alone. There are many studies to suggest that the uremic state per se contributes to the immunoincompetence in CFR [4]. The capacity of the peripheral blood mono-nuclear cells of

CFR patients to produce IL-1 α and IL-1 β was shown to be significantly increased and became comparable with normals 2 months after renal transplantation [11] indicating that the immunoincompetence found in these patients was mainly due to the uremic environment. Based on this evidence, we have attempted to give a booster injection to 5 of the low responders who underwent transplantation. The rationale was that if low responsiveness is attributable to uremia, then its correction by transplantation should have a beneficial effect on the antibody response as well. Since the transplanted population is the subgroup which needs to be specially protected, the significant increase in anti-HBs titer in 4 of these 5 patients was promising. The patient who did not respond to the booster dose of vaccine was 50 years old as compared to those patients who responded (mean age 30 years). Though elderly age has been considered to be a factor for poor antibody response [1], in our study, age was similar between the responders and nonresponders. It is not possible to draw any conclusions in this regard in the posttransplant period based on 1 patient. Even though the transplanted patients were on immunosuppressive therapy they still could mount an effective immune response against vaccine, indicating that the uremia down-regulates the immune response resulting in low response to vaccine. These results are based on a small number of patients and need to be validated in a larger study. Since repeated estimation of anti-HBs antibody titer is expensive and cumbersome, we recommend routine vaccination of all patients entering the HD programme with a double dose of antigen followed by a booster dose to those receiving transplantation as a cost-effective method of providing protection with minimum expenditure.

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