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Immunogenicity of Four Doses of Double-Strength Intramuscular Hepatitis B

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ABSTRACT

***Background*:** Hepatitis B virus potentially accelerates graft rejection and mortality in renal transplantation population. Vaccination of graft candidates without prior immunization against HBV seems essential before transplantation but some candidates of transplantation have not received HBV vaccine at the time of receiving graft. We aimed to evaluate immunogenicity of an enhanced regimen (4 doses of double-strength intramuscular shots) after kidney transplantation in candidates without history of prior HBV vaccination.

***Methods*:** This quasi-experimental study was conducted, 49 renal graft recipients in Sina Hospital (Tehran University of Medical Sciences, Tehran, Iran) of age >18, receiving graft within past 6 months and negative history of hepatitis B vaccination from 2010-2011. Participants received 40 µg intramuscular (IM) shots of a recombinant vaccine in the months 0, 1, 2 and 6. The titer of HBsAb was measured 8 weeks after the 3rd and 4th injections. Cases with HBsAb titers less than 10 mIu/ml were considered as non-responder while antiHBs≥10 mIu/ml was considered protective.

***Results*:** The overall response rate was 57.14% (28/49 patients). Protective HBsAb titers were detected in 44.89% patients following 3rd dose and reached to 57.14% after injecting the 4th shots. The mean HBsAb titers were 50.00 (±88.35) mIu/ml and 229.45 (±356.56) mIu/ml after the 3rd and 4th shots respectively. Responders showed significantly younger age in comparison to non-responders (P=0.013). The vaccine was well tolerated in all patients with no side effects.

***Conclusion*:** Regarding the relative good response rate following HBV vaccination in graft recipients, we suggest a post-transplantation enhanced regimen of 4-dose double-strength IM shots against HBV in patients without prior immunization.

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Introduction

Graft rejection and mortality due to viral infections have remained major problems in organ transplant recipients (1, 2). Infection by hepatitis B virus (HBV) is among those remarkable

infections in renal transplant patients (1-4). The prevalence of hepatitis B in hemodialysis and chronic kidney disease patients varies between countries and even between dialysis units within each country. A study in Tabriz, Iran has calculated a prevalence of 3.2% (5), which is in the range of reported prevalence in western countries (0-10%) (6).

Advances in hepatitis B vaccination have lowered the worldwide prevalence of HBV infection in transplant recipients, for example the incidence of acute HBV infection has declined 75% between 1990 and 2004 (4, 7). HBV infection is distinguished as an independent risk factor for graft failure after renal transplantation with a 2.49 times greater risk for death (8). Thus, either anti-viral therapy for graft recipients with pre-existing HBV infection or vaccination of graft candidates receiving no prior immunization seems essential. Yet, this would improve the clinical outcome, significantly exacerbated by morbidity and mortality of transplantation in endemic regions (2-4, 7, 9). Post-transplantation immunosuppression is a major factor that aggravates HBV replication (10). A multicenter survey has reported the prevalence of post-transplant HBV infection up to 25% (11). This is due to low coverage of and unresponsiveness to vaccination (responsible for 5-10% of cases) (4).

Despite the improved outcome of renal transplantation after conventional vaccination against hepatitis B, only proportions of patients (9%-75%) responded well at 12 months on basis of country, period of administration, age and underlying pathology (8, 12-14). Administration of an enhanced regimen of four doses of double-strength IM vaccination has raised the seroconversion rate, this rate, however, is far from a strong protection (13, 15, 16). As another significant problem in renal transplantation, patients with HBV infection suffer from lack of a uniform efficient management due to clinical complexity and inadequacy of data (11).

Since few studies discussed on the efficacy of post-transplantation vaccination against HBV infection, and some candidates have not received HBV vaccine at the time of receiving graft for some reasons, we aimed to evaluate the immunogenicity of administering four doses of double-strength intramuscular hepatitis B vaccine in renal transplant recipients in a transplantation center in Tehran, Iran.

Patients and Methods

Study population

From 20 March 2010 to 20 march 2011, 4 renal graft recipients in Sina Hospital (Tehran University of Medical Sciences, Tehran, Iran) with: age >18 yr, a history of receiving graft within past 6 months and negative history of hepatitis B vaccination who were clinically stable enrolled in the study. Exclusion criteria included presence of hepatitis B surface antigen (HBsAg), HBsAb, hepatitis B core antibody (anti-HBC), history of hepatitis B vaccination, history of active infection and autoimmune diseases.

The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences, in accordance with the ethical standards laid down in "Declaration of Helsinki 2000" as well as the "Declaration of Istanbul 2008". Written informed consent was obtained from the all participants.

Study protocol

This prospective quasi-experimental clinical trial was conducted at Sina Hospital under "Clinical Trial Registration Code: IRCT201112258514N1". Participants' demographic and clinical characteristics (including duration of dialysis, time of transplantation and received medications) were recorded, as well as titer of virus markers (HBsAb, HBcAb), he-

moglobin, creatinine, CRP, serum albumin and serum iron were measured. All participants received 40 µg IM shots of recombinant HBV vaccine (Euvax B for IM use only, LG Life Sciences, South Korea, LOT number: WVA09029) in deltoid muscle in the months 0, 1, 2 and 6. The length of needle for IM injection was 2.5 cm × 21 gauge (2 cc syringe). Hence, the titer of HBsAb was measured twice at 8 weeks after the 3rd and 4th shots.

Cases with HBsAb titer less than 10 mIU/ml were considered as non-responder; while HBsAb titer ≥10 mIU/ml was considered as adequate protection (seroconversion).

Statistical analysis

We assessed and showed the frequency of variables as number (percentage), and quantitative results as mean (±standard deviation). We applied Chi-square test for comparing qualitative characteristics and Student t-test and/or ANOVA for comparison of quantitative characteristics with normal distribution between two groups; the quantitative characteristics without normal distribution, albeit were analyzed with Mann-Whitney test. All statistical calculations were done with SPSS version 17 (IBM, Armonk, NY). P value <0.05 was considered significant.

Results

After exclusion of 10 participants for absence of the second HBsAb titers (due to lack of adherence to treatment which simply means they did not return for the next shots), 49 eligible patients enrolled in the study. A total 196 shots of double-strength HBV vaccine were delivered. Adverse effects of vaccine (including pain and/or erythema at the site of vaccination, fever, and graft rejection) were observed neither within the first 5 days after inoculation, nor within 12 months

Table 1
Characteristics of responder and non-responder graft recipients receiving hepatitis B vaccine after kidney transplantation

Characteristics		Responder (n=28)	Non-responder (n=21)	P value
Mean age (year)		40.29 (±11.74)	48.76 (±11.00)	0.013
Gender				
	Male	18 (64.28%)	8 (38.09%)	0.07
	Female	10 (35.71%)	13 (61.90%)	
Weight (Kg)		67.92 (±15.06)	69.48 (±13.07)	0.70
Smoking		5 (17.85%)	3 (14.28%)	0.70
Creatinine		1.43 (±0.36)	1.40 (±0.39)	0.76
Hemoglobin		13.30 (±1.15)	12.63 (±3.24)	0.38
Serum iron		88.65 (±34.04)	75.85 (±30.87)	0.20
Serum albumin		4.64 (±0.61)	4.73 (±0.41)	0.55
Positive CRP†		4 (14.28%)	4 (19.04)	0.65
Dialysis duration before transplantation (month)		12.60 (±9.65)	14.67 (±12.31)	0.54
Duration of transplantation (month)		22.04 (±14.01)	26.62 (±26.21)	0.44
Medication				
	Prednisolone (mg/day)‡	7.63 (±13.24)	5.56 (±1.64)	0.49
	Azathioprine (mg/day)	62.50 (±17.68)	-	-
	Cyclosporine (mg/day)	116.96 (±52.73)	107.14 (±31.76)	0.45
	Mycophenolate (mg/day)	1640.00 (±306.87)	1625.00 (±275.06)	0.87

†CRP, C reactive protein; ‡mg, milligram
Frequency of variables and quantitative results are shown as number (percentage) and mean (±standard deviation) respectively.

hence. One-year follow-up of patients for creatinine showed that no one suffered from raise of creatinine through the follow-up period.

Considering the immunogenicity of HBV vaccine, the overall response rate was 57.14% (28/49 patients). Protective HBsAb titers were detected in 22 (44.89%) patients following 3rd dose and reached to 28 (57.14%) after injecting the 4th shots. The mean HBsAb titers were 50.00 (±88.35) mIU/ml and 229.45 (±356.56) mIU/ml for the 3rd and 4th shots respectively.

Table 1 represents study patients' characteristics and their correlation with hepatitis B vaccination. All participants received immunosuppressive medication. The only vaccine administered was HBV. As seen, responders showed significantly lower age in comparison to non-responders (P=0.013).

Discussion

Comparing lower immunogenicity of HBV vaccination in graft recipients with that of normal population suggests the need for a pre-transplantation schedule for vaccination (13, 17, 18). Although some authors have suggested alpha interferon as an adjuvant (19), its administration is a controversial issue because of probability of graft rejection and lack of strongly supporting data. On the other hand, intradermal injection of HBV vaccine is also suggested, but the HBsAb titer rapidly decreases; therefore, an IM booster shot seems mandatory after one year (13). That is why we keep researches on IM injection of HBV vaccine. Numbers of transplantation candidates have not received vaccines in Iran, while this population most likely benefit from this vaccination before renal transplantation. A clinical trial has proposed that a short vaccination protocol against hepatitis B in hemodialysis patients did not provide any benefit compared to the standard approach with respect to HBsAb titers or seroprotection (20). One-year persistence of acquired immunity (with four doses of double-strength IM HBV vaccine) in chronic hemodialysis patients observed in 81.1% of subjects and a antibody titer >100 IU/L was necessary for maintaining a persistent response (21).

The dose of HBV vaccine routinely used in individuals with intact immunity is 20 μg × three times that results in protective antibody titers in 90-95% of cases. On the other hand, response to vaccination is attenuated in graft recipients due to immunosuppression, decreased rate of kidney filtration, serum iron and serum albumin disturbances etc. For this reason, some researchers have proposed an enhanced regimen of four doses of double-strength (40 μg) IM vaccination for raising the seroconversion rate (13, 15, 16). In accordance with patients' age, time of HBsAb measurement and vaccination schedule, antibody titer assessment shows a range of discrepancy. Researchers reported an increased response from 9% with conventional 3-shot inoculation to 36% by means of four doses of double-strength HBV vaccine (15, 16). We achieved a 57.1% response, 8 weeks after the fourth shot of a double-strength dose, which was outstandingly better than others' report. Another study indicated a cumulative response rate of 17.6% at 12 months with three double-strength doses of vaccine (12). Serrano and colleagues pointed out 74.5% response with a similar regimen (14). We may propose the rationale behind these findings: it is perhaps the 4th shot that raises HBsAb titer so far (HBsAb titers were 50.00 (±88.35) mIU/ml and 229.45 (±356.56) mIU/ml for the 3rd and 4th shots respectively) and maintains a persistent immunologic response. Therefore, the 4th shot boosts the immunogenicity of HBV vaccine effectively. Furthermore, the good response in our patients is most likely due to insignificant differences between responders and non-responders' renal characteristics; thus, the insignificant differences between filtration rate, serum iron and serum al-

bumin in two groups did not affect the results.

Investigations concerning immunogenicity of HBV vaccine in renal transplantation are not extensive, when they mostly deal with scheme of HBV vaccine prior to transplantation. In India, completing the hepatitis B vaccination in patients undergone kidney transplantation amid vaccination schedule provided protection in 60%, while partially vaccinated patients developed no immunity (22).

Only a few studies are fulfilled to seek the data for post-transplantation scheme. Lefebure et al compared the result of HBV vaccination before and after renal transplantation. They put forward those four double-strength doses of recombinant HBV vaccine delivered before with a double-strength booster injection after transplantation elevates the response to 86% vs. 36% if given after transplantation (16). This response rate was frankly higher than our finding. Patients' mean age in their investigation was comparable to ours; thus, this characteristic does not rationalize the difference. By the time being, there is no significant predictor for response to vaccination. Jacobson and colleagues found no adverse effect for HBV vaccine (12), so do we similarly.

Conclusion

Although HBV vaccination before renal transplantation leads to the most advantageous results for protection against hepatitis B infection (particularly if a booster dose is administered after procedure), we might recommend an enhanced regimen of four double-strength doses even after transplantation for patients who have not received the proper protection before procedure. Whether the 4th dose maintains a boosted response, spanning months after transplantation is subjected to a follow-up study that is on-hand by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

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