Immune Response of Intradermal Hepatitis B Vaccination at Lower Dose *versus* Intramuscular Vaccination at Double Standard Dose in Predialytic Chronic Renal Failure Patients

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Abstract

The immune responses to hepatitis B vaccine were studied in 2 groups of predialytic chronic renal failure patients who had negative results of hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs) and hepatitis B core antibody (anti HBc). In the intradermal group, vaccine at the dose of 0.1 ml, 2 μg, was intradermally administered at 5 positions. In the intramuscular group, the vaccine at the dose of 1.0 ml, 20 μg, was intramuscularly given at 2 positions and, thus, was a double standard dose. Both groups received 4 vaccinations at month 0, 1, 2, and 6 (M0, M1, M2, and M6). The results showed that there were no significant differences in the results of seroconversion rates, defined as having anti HBs levels above 10 mIU/ml, between the intradermal (ID) and intramuscular (IM) groups at M1, M2, M6, and M7. In patients with positive seroconversion results at M7, the numbers of patients in the good and excellent subgroups, having HBs Ab levels ranged 10-999 and above 1,000 mIU/ml respectively, showed no difference between both routes. The body weight and seroconversion rates at M2 and M6 were the factors which had a positive influence on the seroconversion rates of intradermal hepatitis B vaccination. In conclusion, intradermal hepatitis B vaccination at a lower dose could provide comparable satisfactory immune response with the intramuscular route at double the standard dose.

Key word : Hepatitis B Vaccination, Intradermal Route, Intramuscular Route

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Because of impairment in cell-mediated immunity[1,2], the seroconversion rates following hepatitis B vaccination were only 32.5 to 67 per cent in patients with chronic renal failure[3-6], compared with above 90 per cent in normal subjects[7-9]. More over, hepatitis B vaccination in post kidney transplantation patients has yielded only 36 per cent of positive immune response[10]. Increasing dosage as well as frequency of vaccination in dialysis patients[11,12] could enhance the per cent of the seroconversion rate to the range of 70 to 90 per cent[5-7,13-18]. According to the recommendation of "Center of Disease Control", all uremic patients should receive intramuscular hepatitis B vaccination at a double standard dosage of recombinant DNA vaccine and with increased frequency from 3 (month 0, 1, and 6), to 4 (month 0, 1, 2, and 6) times[19].

Recently, there have been several intradermal hepatitis B vaccination studies in hemodialysis patients reporting comparable immune responses with the intramuscular route[8,9,20-23]. The dose of vaccine used in the former is much lower than the latter. In pre dialysis patients, the immune response would be less impaired than the dialysis as well as post kidney transplantation patients[24-27], and, thus, would have a salutary immune response to intradermal hepatitis B vaccination.

The present study was conducted to compare the immune response of intradermal hepatitis B vaccination at a lower dose *versus* intramuscular vaccination at double the standard dose in predialytic chronic renal failure.

PATIENTS AND METHOD

Patients

The study was approved by the Ethical Committee, Faculty of Medicine, Chulalongkorn University. Informed consent was obtained from each patient. This prospective randomized control trial study was performed on predialysis patients who were treated at King Chulalongkorn Memorial Hospital, Bangkok Thailand. Inclusion criteria were 1) age less than 85 years 2) serum creatinine ranged from 3-8 mg/dL 3) serum albumin at least 3.5 g/dL 4) the results of HBsAg, anti HBs, and anti HBc, determind by ELISA method (Cobas® core Roche), showing "negative" 5) not receiving hepatitis B vaccination. Exclusion criteria comprised 1) having malignancy or chronic infection, including tuberculosis and human immune deficiency virus, during the study; 2) receiving immunosuppressive agents; 3) having serious side effects from vaccination; 4) decrease of serum creatinine below 3 mg/dL; 5) progression to end stage renal disease and receiving dialysis.

Method

The hepatitis B vaccine used in the present study was Engerix B®. The participating patients were divided by simple randomization into 2 groups.

1. Intradermal or ID group. The vaccine at the dose of 0.1 ml, 2 μg, was intradermally administered at 5 positions. The total dose of each ID vaccination was 10 μg/patient.

2. Intramuscular or IM group. The vaccine at the dose of 1.0 ml (20 μg) was given at intramuscularly 2 positions. The total dose of each IM vaccination was 40 μg/patient. Patients in both the ID and IM groups received 4 vaccinations (month 0, 1, 2, and 6). As such, the total doses of hepatitis B vaccine prescribed were 40 and 160 μg/patient in ID and IM groups, respectively.

The levels of anti HBs were determined at 1, 2, 6, and 7 months after the first vaccination, month 0. The results of anti HBs levels above 10 mIU/ml were considered as "positive" and as the effectively protective titer for hepatitis B infection. The "negative" results were reported when the anti HBs levels were below 10 mIU/ml.

Patients with positive results were further categorized into 2 subgroups, the good and excellent immunologic responses. The former had anti HBs levels ranging 10-999 mIU/ml while the antibody levels in the latter were above 1,000 mIU/ml.

Statistical analysis

"Independent sample *t*-test" was used to compare the numerical data while "Chi-Square test" was employed to compare the ordinary data. "Logistic regression analysis" was utilized to asses the variables affecting the seroconversion rate. All data in the Tables and figures are presented as mean ± SD and $p < 0.05$ was considered statistically significant.

RESULTS

Demographic data

There were 21 and 19 predialysis patients in the ID and IM groups, respectively. As seen in Table 1, there were no statistically significant differences in demographic data between the two groups. Thus, there was no bias in sampling the patients into ID or IM group.

Table 1 Baseline demographic, clinical, and laboratory data between the intradermal (ID) and intramuscular (IM) groups.

	ID (n = 21)	IM (n = 19)	P-value
Male : female	10 : 11	4 : 15	0.1
Age (years)	59.7 ± 12.8	60.0 ± 14.0	0.1
Serum creatinine (mg/dL)			
Prior to vaccination	4.6 ± 0.28	4.4 ± 0.3	0.67
Post vaccination	5.8 ± 0.4	5.4 ± 0.4	0.7
Diabetes (%)	19	42	0.2
Body weight (kg)	60.3 ± 7.37	61.0 ± 11.8	0.1
Serum albumin (g/dL)	4.3 ± 0.3	4.1 ± 0.5	0.1
Hematocrit (%)	31.4 ± 1.0	31.0 ± 0.9	0.1

The data were expressed as mean ± SD

Table 2. Comparison of seroconversion rates between intradermal (ID) and intramuscular (IM) groups at different time points.

Seroconversion rate	ID (%)	IM (%)	P-value
M1	14.3	15.8	0.95
M2	33.3	63.2	0.12
M6	61.9	84.2	0.31
M7	85.7	89.6	0.7

Seroconversion rate

Table 2 depicts the results of the seroconversion rates of the patients in both groups at month 1, 2, 6, and 7 (M1, M2, M6, and M7) after the first vaccination, M0. No significant differences in the results of seroconversion rates were observed between the ID and IM groups at any time points. (Chi Square test)

In patients with positive seroconversion results at M7, the number of patients in the good and excellent subgroups who received ID vaccination did not differ from the IM vaccination-administered patients (Table 3). (NS, Chi Square test)

Factors influencing the seroconversion rate

As illustrated in Table 4, the body weight and seroconversion rates at M2 and M6 were the factors which had a positive influence on the seroconversion rates of the intradermal hepatitis B vaccination.

DISCUSSION

Although there have been several studies of intradermal (ID) hepatitis B vaccination in uremic patients, most were performed on dialysis patients (8,9,20-23). Data regarding the effectiveness of ID hepatitis B vaccination in predialytic patients with chronic renal failure is scarce. At M7, 1 month after completion of the vaccination course, the seroconversion rates in the ID group in the present work were 85.7 per cent, which did not differ from the intramuscular (IM) group (Table 2). Of interest, the dose of hepatitis B vaccine in the ID group was one-fourth of the IM group. The values of the seroconversion rate in the ID group in the current work were higher than 61 per cent obtained in dialysis patients in a recent ID vaccination study which had a similar dosage and regimen as the present study(28).

The excellent immune response with less vaccine in ID hepatitis B vaccination might be explained by several mechanisms. Firstly, intradermis is a dense tissue which can bind antigen longer than the intramuscular layer(15,16). Secondly, intradermis, not intramuscular layer, has Langerhan's cells which have the ability to present antigen to T lymphocyte, leading to an enhanced immune response(29-31). Lastly, delayed type hypersensitivity, a subtype of cell mediated immunity, is the main immune response to several intradermal vaccinations, besides hepatitis B, including tuberculosis, typhoid, diptheria, cholera, influenza and rabies(32-34). Furthermore, several studies have demonstrated that intradermal hepatitis B vaccination could reactivate immune response in uremic patients who did not respond to intramuscular vaccination route(16,20,35,36).

Although the statistical significance was not attained, the ID group had a trend to have lower seroconversion rates and fewer patients with excellent response when compared with the IM group (Table 2

Table 3. Comparison of good and excellent responses between intradermal (ID) and intramuscular (IM) groups at month 7.

Subgroup response	ID (%)	IM (%)	P-value
None	14.3	10.5	0.1
Response			
Good (10-999 mIU/ml)	52.4	26.3	0.1
Excellent (> 1,000 mIU/ml)	33.3	63.2	0.1

Table 4. Factors influencing the seroconversion rates of the intradermal hepatitis B vaccination.

	P-value	R
Gender	0.92	0.0
Age	0.26	0.0
Serum creatinine levels prior to vaccination	0.97	0.0
Serum creatinine levels after vaccination	0.71	0.0
Diabetes	0.24	0.0
Body weight	0.0001	0.63
Serum albumin	0.09	0.12
Hematocrit	0.43	0.0
Seroconversion rate at M1	0.9	0.0
Seroconversion rate at M2	0.01	0.36
Seroconversion rate at M6	0.000	0.70

and 3). This might be explained by the much lower dose of hepatitis B vaccine used in the ID group. Results from several previous studies in hemodialysis patients have supported such contention. Prost et al intradermally administered a total dose 100 μgm of Engerix B, at a dose of 20 μgm every 2 weeks, and could induce the seroconversion rate of 94 per cent (20). A recent study by Andre et al demonstrated the Engerix B at a dose of 5 μgm intradermally given every 2 weeks could provide an excellent seroconversion rate of 97.6 per cent in 8 months(13). The average vaccine dose was 40.5 ± 4.8 μgm. To reach the anti HBs levels above 1,000 mIU/ml, the amount of vaccine was 109.8 ± 10.4 μgm and the total vaccination time was 12.7 ± 1.1 months.

The comparable seroconversion rate between the ID and IM routes occurs in association with the four times lower cost of the ID route. This would underscore the superiority of the cost-effectiveness of the ID hepatitis B vaccination.

In conclusion, in the 6-month study of predialysis patients, intradermal hepatitis B vaccination at a lower dose could induce a comparable immune response with the intramuscular route at double the standard dose. This would offer an effectively alternative method of hepatitis B vaccination in uremic patients. Further studies are needed to enhance the effectiveness of the intradermal hepatitis B vaccination.

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การตอบสนองภูมิคุ้มกันต่อการให้วัคซีนไวรัสตับอักเสบชนิดบีทางผิวหนัง ในขนาดต่ำเทียบกับทางกล้ามเนื้อในขนาดสองเท่าของขนาดมาตรฐานในผู้ป่วยไตวายเรื้อรังระยะก่อนล้างไต

วนิดา สมบูรณ์ศิลป์, พบ, สมชาย เอี่ยมอ่อง, พบ**, เกรียง ตั้งสง่า, พบ**, ทวีศักดิ์ ตีระวัฒนพงษ์, วทด****

ทำการศึกษาการตอบสนองภูมิคุ้มกันต่อวัคซีนไวรัสตับอักเสบชนิดบีในผู้ป่วยไตวายเรื้อรังระยะก่อนล้างไตที่ไม่มีภูมิคุ้มกัน กลุ่มแรกได้วัคซีนในชั้นผิวหนัง 5 ตำแหน่ง ๆ ละ 0.1 มิลลิลิตร หรือ 2 ไมโครกรัม กลุ่มที่สองได้วัคซีนในชั้นกล้ามเนื้อ 2 ตำแหน่ง ๆ ละ 1.0 มิลลิลิตร หรือ 20 ไมโครกรัม กลุ่มที่สองจึงได้รับวัคซีนเป็นสองเท่าของขนาดมาตรฐาน ทั้งสองกลุ่มได้รับวัคซีน 4 ครั้งคือ เดือนที่ 0, 1, 2 และ 6 ผลการศึกษาพบว่าไม่มีความแตกต่างในการตอบสนองภูมิคุ้มกันต่อวัคซีนระหว่าง 2 กลุ่มที่เดือนที่ 1, 2, 6, และ 7 ในผู้ป่วยที่มีการตอบสนองภูมิคุ้มกันพบว่าไม่มีความแตกต่างของจำนวนผู้ป่วยที่มีระดับภูมิคุ้มกันดีและดีมาก (10–999 และมากกว่า 1,000 มิลลิอินเตอร์เนชันแนลยูนิต/มิลลิลิตร ตามลำดับ) ระหว่าง 2 กลุ่มที่เดือนที่ 7 พบว่าน้ำหนักและการตอบสนองภูมิคุ้มกันที่เดือนที่ 2 และ 6 เป็นปัจจัยบวกต่อการตอบสนองภูมิคุ้มกันต่อการให้วัคซีนทางใต้ผิวหนัง กล่าวโดยสรุป การให้วัคซีนไวรัสตับอักเสบชนิดบีในขนาดต่ำสามารถกระตุ้นภูมิคุ้มกันได้เป็นผลที่น่าพอใจ ไม่แตกต่างจากการให้ทางกล้ามเนื้อในขนาดสองเท่าของขนาดมาตรฐาน

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