Efficacy of Intradermal Hepatitis B Vaccination Compared to Intramuscular Vaccination in Hemodialysis Patients

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Background: *Hepatitis B virus infection remains an important problem in hemodialysis patients. Only 50 to 60% of the patients develop seroconversion (anti-HBs Ab titer > 10 IU/L) after intramuscular hepatitis B vaccination. Small dose intradermal inoculation method of hepatitis B vaccine has been reported to be effective as well as economical, and could provide rapid seroconvesion of immunity. The aim of the present study was to compare the efficacy of intradermal hepatitis B vaccination with intramuscular vaccination in hemodialysis patients.*

Material and Method: *Fifty one hemodialysis patients were randomly assigned to two groups, 25 patients received a total 7 doses of 10 mμg of recombinant hepatitis B vaccine (Engerix B) intradermally every 2 weeks (ID group), whereas 26 patients received 40 μg intramuscularly at 0, 1, 2 and 6 months (IM group). Anti-HBs Ab titer was measured at 2, 3, 4 and 7 months after the first vaccination in both groups. Vaccination responses were classified into 3 subgroups according to anti-HBs Ab titer and these included excellent response (≥ 1,000 IU/L), good response (10 - 999 IU/L) and non-response (< 10 IU/L).*

Results: *The seroconversion rates at 2, 3, 4, and 7 months in the ID group were 56%, 76%, 88%, and 92% compared with 31%, 42%, 65%, and 69% in the IM group, respectively. Only the seroconversion rates at 3 months were significantly higher in the ID group (76% versus 42%, p = 0.03). At 7 months after the first vaccination, good and excellent responders in the ID group were 72% (18/25) and 20% (5/25) compared with 34.5% (9/26) and 34.5% (9/26), respectively (p > 0.05). Only minor side effects were observed.*

Conclusion: *Seven doses of 10 mg intradermal vaccination induced a high seroconversion rate and were comparable with intramuscular regimen. Intradermal vaccination may be helpful for the rapid induction of protective level of antibodies and may be a cost-saving alternative to intramuscular vaccination in hemodilaysis patients.*

Keywords: *Immune response, Intradermal Hepatitis B Vaccination, Hemodialysis*

J Med Assoc Thai 2006; 89 (Suppl 2): S33-40
Full text. e-Journal: *http://www.medassocthai.org/journal*

Hepatitis B virus (HBV) infection in hemodialysis patients remains an important problem. Hemodialysis patients are at high risk of acquiring infection. Unlike healthy adults, HBV infection in patients undergoing hemodialysis become chronic in 30 to 60%, compared with less than 10% in nonuremic patients[1-4]. Moreover, those with acute HBV infection usually have a mild, asymptomatic disease, but they may spread readily to other patients and staff of the dialysis unit[4]. The most important factor to prevent the spread of HBV is the maintenance of universal precaution. In addition, CDC recommends[5] isolating hepatitis B surface antigen (HBsAg) positive patients, treatments by a separate nursing team and hemodialysis machine, prohibiting the use of shared medications in the dialysis unit, no reused dialyzer strategy, and given hepatitis B (HB) vaccination to all seronegative patients. A recent case-control study[6] in hemodialysis patients found that the risk for HBV infection was 70% lower in

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vaccinated than in unvaccinated patients (adjusted odds ratio, 0.3; 95%CI, 0.18-0.5). However, only 50 to 60% of hemodialysis patients develop seroconversion (anti-HBs Ab > 10 IU/L) after a primary intramuscular hepatitis vaccination (40 g; 3 injections)[7-10]. Moreover, after completion of the vaccination schedule anti-HBs antibody titers of responder dialysis patients are low and fall rapidly[11].

Suboptimal response to hepatitis B vaccination is attributed to suppressed immunity in advanced chronic kidney disease patients. Other host factors that have been implicated in lack of response to HB vaccination[12] including older age, male gender, obesity, a history of blood transfusion, hepatitis C virus (HCV) infection, poor nutritional status and inadequate dialysis. Several approaches have been tried to increase the seroconversion rate and duration of immunity including an increase in the number of doses, increase in the antigen load per dose, use of intradermal route, adding interleukin-2 to the protocol, and considering vaccination earlier during the evolution form of chronic kidney disease to end-stage renal disease. Current recommendations for enhancing responsiveness to HB vaccination in dialysis patients[5] are administering a double dose of vaccine 40 g dose of Recombivax HB in a three-dose schedule at 0, 1, and 6 months; or two 20 g standard dose of Engerix-B in a four-dose schedule at 0, 1, 2, and 6 month. However, the high cost of plasma-derived and recombinant HB vaccine is an obstacle to extensive immunization against HBV infection. Smaller dose and more frequent intradermal inoculation method of HB vaccine have been reported to be effective and rapid seroconversion of immunity with a lower cost. However, the dosages, schedule, and the response rates have been varied. The aim of this prospective randomized trial was to assess the efficacy of intradermal HB vaccination compared to intramuscular HB vaccination.

Material and Method

Hemodialysis patients in the chronic hemodialysis program at Siriraj Hospital (Bangkok, Thailand) from May 2002 to February 2004 were recruited into the present study. To be eligible, patients were required to be HBsAg negative, antibody to HBsAg (anti-HBs Ab) negative and antibody to HBc (anti-HBc) negative. The patients who had active infection, human immunodeficiency virus infection, malignancy or receiving immunosuppressive drugs were excluded. The present study was approved by the ethic committee. After informed consent was obtained, patients were randomly assigned to either intramuscular (ID) or intradermal (IM) HB administration. The vaccine used in the present study was recombinant HB vaccine (Engerix B; Smith Kline Beecham Pharma Inc). Patients randomized to IM vaccination were administered HB vaccine 40μg, as a 1-mL (20 μg) IM injection in each deltoid region predialysis at interval of 0, 1, 2, and 6 months. Those randomized to ID vaccination received 10 μg (0.5 mL) HB vaccines every 2 weeks for a total of 7 doses. Vaccine was administered intradermally with insulin syringe with a 30-gauge needle as a 0.25-mL (5μg) x 2 sites in the lateral aspect of the upper arm. Wheal formation confirmed that the ID injection had been effective. The presence of a cutaneous bleb and side effects were documented.

On entry, the following data were collected, age, sex, smoking status, diabetes, previous transplant, previous blood transfusion, anti-Hepatitis C Virus Antibody (anti-HCV Ab), duration of dialysis in months, Hematocrit ((Hct) level, use of erythropoietin, dosage of erythropoietin, dialysis adequacy (Kt/V), and nutritional status (serum albumin level, normalized Protein Catabolic Rate (nPCR), and Body Mass Index (BMI)). Antibody to HBsAg titers was measured at 2, 3, 4, 7 months after the first vaccination in both groups (Fig. 1). Seroconversion was defined as anti-HBs Ab titer 10 IU/L or more. Vaccination responses were classified into 3 subgroups according to anti-HBs Ab titer included excellent immune response ($\geq$ 1,000 IU/L), good immune response (10 - 999 IU/L) and non-response (< 10 IU/L).

Statistical analysis was performed using SPSS for Windows v10.0. The data were expressed as mean $\pm$ SD or percentage. The data were compared for the difference of mean between groups by student t-test and different of proportion by chi-square test. A p of < 0.05 was accepted as significant.

Results

From May 2002 to February 2004, 210 hemodialysis patients were screened for HB viral profiles. Fifty-two patients fulfilled the inclusion criteria and were randomly assigned to treatment, 26 patients to ID vaccination and 26 to IM vaccination. One patient in the ID group was excluded due to death from infection before completing the study protocol. The patient characteristics assigned to treatment with ID (n = 25) and IM vaccination (n = 26) are listed in Table 1. The mean duration of hemodialysis treatment was not statistically different between the groups (62.5 vs 69.5 months, p = 0.12). Patients were similar in every parameter. These included sex, diabetes, frequency of anti-HCV Ab, hematocrit level, erythropoietin dosage,

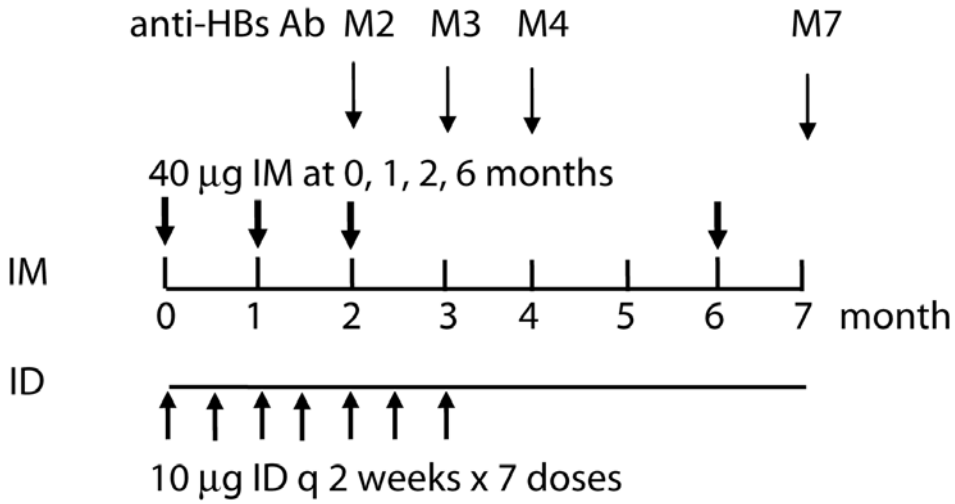

Fig. 1 Intramuscular and intradermal HB vaccine schedule and timing of anti-HBs Ab titer measurement

previous blood transfusion, frequency of anti-HCV Ab, nutritional parameters (serum albumin, nPCR, BMI) and dialysis adequacy except for age, which was slightly higher in the IM group (41 ± 16 versus 50 ± 17 years; p = 0.04).

Seroconversion rates at 2, 3, 4, 7 months after the first vaccination

The seroconversion rates at 2, 3, 4, 7 months after the first vaccination in the ID group and in the IM group are shown in Table 2. There was no difference in seroconversion rates at the same times in both groups except for the seroconversion rates at 3 months which was significantly higher in the ID group (76% versus 42%; p = 0.03). The seroconversion rate at 7 months in the ID group was 92% (23 of 25 patients) compared with 69% (18 of 26 patients) in the IM group (p = 0.08). Immunological responses in the responders in both groups were classified into excellent responses (anti-HBs Ab ≥ 1000 IU/L) and good responses (anti-HBs Ab 10-999 IU/L) as shown in Fig. 2. The excellent immunological responses at 2, 3, 4, 7 months were not significantly different in both groups (p > 0.05). At 7 months after the first HB vaccination, good responders and excellent responders in the ID group were 72% (18/25) and 20% (5/25) compared with 34.5% (9/26) and 34.5% (9/26) in the IM group (p > 0.05), respectively (Fig. 2).

Table 1. Characteristics of patients randomized to treatment with ID or IM vaccination

	Intradermal	Intramuscular	p value
No. of patients	25	26	
Age (years)	41±6	50±17	0.04
Sex: Male (%)	44	61	0.33
Diabetes (%)	16	19	1.00
Body mass index (kg/m^2)	20.8	19.9	0.15
Previous blood transfusion (%)	33.3	30.8	0.50
Hematocrit (%)	28±7	29±6	0.60
Erythropoietin (%)	27.5	30.8	0.90
Erythropoietin dose (IU/week)	4,807±1,800	5,400±2,200	0.20
Previous hepatitis vaccination (%)	28	35	0.18
anti-HCV Ab (%)	8.0	7.7	1.00
Kt/V	1.8±0.3	2.0±0.4	0.43
Serum albumin (gm/dL)	4.1± 0.4	4.0±0.5	0.50
Normalized protein catabolic rate (gm/kg/day)	1.0±0.2	1.1±0.2	0.13

Table 2. The seroconversion rates at 2, 3, 4, 7 months after the first vaccination

months after the first vaccination	Seroconversion rate (%)		p value
	Intradermal (n = 25)	Intramuscular (n = 26)	
2	56	31	0.13
3	76	42	0.03
4	88	65	0.12
7	92	69	0.08

Seroconversion was defined as anti-HBs Ab titer > 10 IU/L

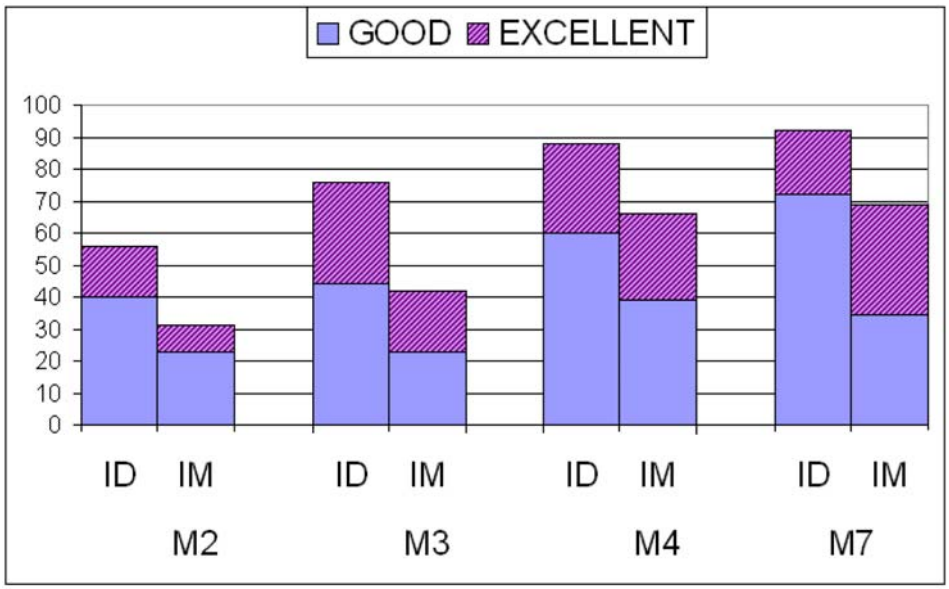

Fig. 2 Seroconversion rates and immunological responses subgroup at 2 (M2), 3 (M3), 4 (M4), 7 (M7) months after the first vaccination in intradermal (ID) and in intramuscular (IM) were shown. Excellent immunological responses (anti-HBs Ab $\geq$ 1000 IU/L) are represented by the cross hatched bars, and good immunological responses (anti-HBs Ab 10-999 IU/L) by the black bars

Previously received hepatitis B vaccination and seroconversion rates

Twenty-one patients in the ID group and seventeen patients in the IM group had never previously received HB vaccination. The seroconversion rates in these patients are shown in Table 3. There were no differences in seroconversion rates at 2, 3, 4, 7 months after the first HB vaccination in both groups. At the end of the study (7 months), seroconversion rate in the ID group was 90% (19/21) compared with 82% (14/17) in IM group (p = 0.16).

Four patients in the ID group and nine patients in the IM group had previously received intramuscular vaccination but never had a protective antibody. At 7 months after revaccination, all patients (4/4) in the ID group had a protective level of anti-HBs titer compared with 87% (7/9) in IM group (p > 0.05).

Cost and side effect

Although the seroconversion rates in both groups were comparable, the total cost for the ID regimen in the present study was only half of the IM regimen since the total intradermal dose was only 44% of the intramuscular vaccination regimen. Each intradermal injection of 5 μg (0.25 ml) vaccine caused a bleb diameter average 5 mm (up to 1 cm)[23] but this was acceptable to all patients. Skin reactions after intradermal vaccination at the inoculation site consisted of

Table 3. The seroconversion rates in patients who never previously received hepatitis B vaccination

months after the first vaccination	Seroconversion rate (%)		p value
	ID (n = 21)	IM (n = 17)	
2	52	41	0.72
3	71	53	0.40
4	85	76	0.43
7	90	82	0.16

erythematous, sometimes indurated macules that faded over a period of days or weeks. There were no systemic symptoms in any of the presented patients.

Discussion

Compared to a response rate of over 90% in a healthy population, only 50% to 60% of hemodialysis patients develop protective antibodies after vaccination[7]. Suboptimal response to the vaccination is attributed to suppressed immunity in advanced chronic kidney disease patients with qualitative and/or quantitative defect in lymphocyte, macrophages and dendritic cells[13-16]. Recent evidence on the cellular level[17] demonstrated that HBV-specific humoral and cellular immune responses can be enhanced in healthy individuals via primary T- and B-cell stimulation by dendritic Langerhans cells of the dermis by using ID route of HB vaccination. Several studies in hemodialysis patients have shown that intradermal vaccination is effective, economical, and rapid seroconverion of immunity[4,18-21]. Ono et al[18] reported a response rate of 98% five months after the initial vaccination of 5 mg ID every 2 weeks with mean amount of HBs Ag of 25.0 $\pm$ 4.2 mg. However, anti-HBs Ab titers in the present study were low (< 100 IU/L), and a rapid decline of anti-HBs Ab titer occurred after the last vaccine injection. Propst et al[4] reported that a higher ID injection dose (20 g) with a mean of five vaccine injections had a response rate of 94%, which was superior to IM and SC vaccination response. The protective anti-HBs Ab level persisted in 70% of the patients over 3 years[4].

Compared with previous studies (Table 4), the present study showed that 7 doses of 10 g ID vaccination schedule could achieve a high seroconversion

Table 4. Comparison of seroconversion rates in hemodialysis patients after intradermal or intramuscular hepatitis B vaccination in previous studies and the present study

References	No. of patients	Vaccination route and dosage schedule	vaccination dosage (g)	No. of injections	Response rates (%)
Ono et al[18]	14	ID 5 g q 2 wks	25$\pm$4.2	5	100
Mettang et al[21]	14	IM 40 g at 0, 1, 3, 6 mos	160	4	64
	18	ID 10 g at 0, 1, 3, 6 mos	40	4	61
Fabrizi F et al[23]	25	IM 40 g at 0, 1 mo	80	2	40
	25	ID 5 g q 1 wk x 16 doses	80	16	96
Propst et al[4]	27	IM 40 g at 0, 1, 6 mo and booster at 8, 12 mos (max. 200 g)	160	4	76
	27	SC 20 g q 2 wks	100	5	69
	27	ID 20 g q 2 wks until seroconversion (max. 240 g)	100	5	94
Charest et al[20]	40	IM 40 g at 0, 1, 2, 6 mos	160	4	90.5
	41	ID 5 g q 2 wks* (max. 52 doses)	57$\pm$6.5	7 (median)	97.4
Roozbeh et al[22]	20	IM 40 g at 0, 1, 4 mos	120	3	50
	26	ID 20 g at 0, 1, 4 mos	60	3	50
The present study	26	IM 40 g at 0, 1, 2, 6 mos	160	4	69
	25	ID 10 g q 2 wks x 7 doses	70	7	92

* until the patient either developed an antibody titer >1,000 IU/L or maximal 52 doses

rate of 92%, which is comparable with data from Propst et al[4] (94%) and Charest et al[20] (97%) but greater than the rate of Mettang et al[21] (61%), who used a smaller antigen load (5 μg ID at 0, 1, 2 and 6 months). The total dose of ID vaccination needed to induce a high seroconversion rates range from 60-100 μg (Table 4). However, the vaccine schedule is also important as shown in the Roozeh et al study[22] that only 50% seroconversion rate was observed with ID regimen of 20 μg at 0, 1, and 4 months.

Although the mean age of patients in the IM group was slightly older than in the ID group, the seroconversion rate in the IM group was 69%, which is comparable with data from Mettang et al[21] and Propst et al[4]. They both used a similar regimen. The present study did not show a significant difference in either serconversion rate or excellent response of immunity between the two routes of vaccination. However, the ID route achieved seroconversion earlier than the IM route. Seventy six percent of patients in the ID group developed a protective antibody levels within 3 months, compared with 42% in the IM group. The presented data, was in agreement with previous studies[23,24] and, showed that the intradermal route is also an effective method of vaccination against HB in primary non-responding hemodialysis patients. However, there are some disadvantages when using ID vaccinations, including the requirement for skillful administration (injection into subcutaneous leads to a poor response, worst than the IM route), the development of local skin reactions, a lower antibody response when using inappropriate ID vaccination regimens (including the vaccine dosage, and vaccination schedule) and the more rapid decline in Ab titers than the IM route.

In conclusion, the results of the present study indicated that 7 doses of ID injections of 10 g HB vaccine induced seroconversion in 92% of hemodialysis patients, with vaccination cost reduced by half of that in the IM regimen. Intradermal administration may also be helpful for the rapid induction of antibodies and reversing non-responsiveness.

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ประสิทธิภาพของการฉีดวัคซีนป้องกันไวรัสตับอักเสบบีเข้าชั้นผิวหนังและการฉีดเข้าชั้นกล้ามเนื้อในผู้ป่วยโรคไตวายเรื้อรังที่ได้รับการฟอกเลือดด้วยเครื่องไตเทียม

ทวี ชาญชัยรุจิรา, นฤมล จันทาภากุล, ทวีศักดิ์ แทนวันดี, ลีนา องอาจยุทธ

ที่มา: *การติดเชื้อไวรัสตับอักเสบบียังเป็นปัญหาสำคัญในผู้ป่วยไตวายเรื้อรังที่ได้รับการฟอกเลือด ผู้ป่วยกลุ่มนี้มีการตอบสนองทางภูมิคุ้มกันภายหลังการฉีดวัคซีนไวรัสตับอักเสบบีเข้าชั้นกล้ามเนื้อเพียงร้อยละ 50-60 การฉีดวัคซีนเข้าชั้นผิวหนังในขนาดต่ำเคยมีรายงานว่ามีประสิทธิภาพดี ประหยัดค่าใช้จ่ายและใช้เวลาในการตอบสนองน้อยกว่า การศึกษานี้มีวัตถุประสงค์เพื่อเปรียบเทียบประสิทธิภาพของการฉีดวัคซีนและระยะเวลาของการตอบสนองภูมิคุ้มกันระหว่างการฉีดเข้าชั้นผิวหนังและชั้นกล้ามเนื้อในผู้ป่วยไตวายที่ได้รับการฟอกเลือด*

วัสดุและวิธีการ: *ผู้ป่วยที่ได้รับการฟอกเลือดจำนวน 51 ราย ถูกแบ่งโดยการสุ่มออกเป็น 2 กลุ่ม กลุ่มที่ 1 (25 ราย) ได้รับการฉีดวัคซีน (recombinant hepatitis B vaccine; Engerix B) เข้าชั้นผิวหนังในขนาด 10 ไมโครกรัมทุก 2 สัปดาห์จนครบ 7 ครั้ง กลุ่มที่ 2 (26 ราย) ได้รับการฉีดวัคซีน 40 ไมโครกรัมเข้าชั้นกล้ามเนื้อในเดือนที่ 0, 1, 2 และ 6 ผู้ป่วยทุกรายได้รับการตรวจระดับภูมิคุ้มกันในเดือนที่ 2, 3, 4 และ 7 หลังฉีดวัคซีนเข็มแรก เปรียบเทียบระดับภูมิคุ้มกันของ ผู้ป่วย 2 กลุ่ม โดยแบ่งระดับการตอบสนองออกเป็น 3 กลุ่ม กลุ่มแรกตอบสนองดีเยี่ยม (anti-HBs Ab $\geq$ 1000 IU/L) กลุ่มที่สองตอบสนองดี (10-999 IU/L) และกลุ่มที่สาม ไม่ตอบสนอง (< 10 IU/L)*

ผลการศึกษา: *ระดับภูมิคุ้มกันต่อไวรัสตับอักเสบบีที่ป้องกันโรคได้ (anti-HBs Ab $\geq$ 10 IU/L) ในเดือนที่ 2, 3, 4 และ 7 ของกลุ่มที่ได้รับวัคซีนเข้าชั้นผิวหนังเท่ากับร้อยละ 56, 76, 88 และ 92 เทียบกับ กลุ่มที่ได้รับวัคซีนเข้าชั้นกล้ามเนื้อเท่ากับร้อยละ 31, 42, 65 และ 69 ตามลำดับ การตอบสนองทางภูมิคุมกันนี้ไม่แตกต่างกัน ยกเว้นในเดือนที่ 3 ซึ่งในกลุ่มที่ได้วัคซีนเข้าชั้นผิวหนังมีการตอบสนองทางภูมิคุ้มกันดีกว่าชัดเจน (76% vs 42%, p = 0.03) เมื่อสิ้นสุดการศึกษาที่เดือนที่ 7 พบว่า ในกลุ่มได้วัคซีนเข้าชั้นผิวหนัง ระดับของภูมิคุ้มกันของผู้ป่วยที่มีการตอบสนองดี และดีเยี่ยมเท่ากับร้อยละ 72 (18/25), 20 (5/25) ตามลำดับ เทียบกับ ร้อยละ 34.5 (9/26), 34.5 (9/26) ในกลุ่มที่ได้วัคซีนเข้าชั้นกล้ามเนื้อ โดยไม่มีความแตกต่างทางสถิติ (p > 0.05) ไม่พบผลข้างเคียงร้ายแรงใด ๆ หลังฉีดวัคซีนในผู้ป่วยทั้งสองกลุ่ม*

สรุป: *การฉีดวัคซีนเข้าชั้นผิวหนังในผู้ป่วยไตวายเรื้อรังที่ได้รับการฟอกเลือด โดยใช้ฉีดวัคซีนขนาด 10 ไมโครกรัม รวม 7 ครั้งพบว่า ได้ผลการตอบสนองทางภูมิคุ้มกันที่ดี โดยได้ผลไม่แตกต่างกับการให้วัคซีนเข้าทางกล้ามเนื้อ แต่การให้วัคซีนเข้าชั้นผิวหนังใช้เวลาสั้นกว่าในการทำให้ถึงระดับภูมิคุ้มกันที่ป้องกันโรคได้ เมื่อเทียบกับการฉีดวัคซีนเข้าชั้นกล้ามเนื้อ แม้ว่าการตอบสนองทางภูมิคุ้มกันไม่แตกต่างกันแต่การฉีดวัคซีนเข้าชั้นผิวหนังใช้ปริมาณวัคซีนน้อยกว่า ดังนั้นการฉีดวัคซีนป้องกันไวรัสตับอักเสบบีเข้าชั้นผิวหนังอาจเป็นทางเลือกหนึ่งในแง่ประสิทธิภาพ สามารถลดค่าใช้จ่ายและมีผลข้างเคียงต่ำ*