A Randomized Controlled Trial of Seroconversion After 20 Mg versus 40 mg Intramuscular Hepatitis B Virus Vaccination in Patients with Chronic Kidney Disease Stage 3

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Background: *There is as yet no guideline for hepatitis B virus (HBV) vaccination in chronic kidney disease (CKD). There is also insufficient evidence to support the theory that the immune response to a double dose (40 μg) of HBV vaccine is greater than that achieved by the standard dose (20 μg).*

Objective: *To compare seroconversion of the four-dose regimen (at 0, 1, 2, 6 months) of intramuscular recombinant DNA HBV vaccination using the standard 20 μg with that of 40 μg in patients with CKD stage 3.*

Material and Method: *This study included 39 patients with CKD stage 3 who had neither history of HBV vaccination nor markers of HBV infection, namely hepatitis B surface antigen (HBs Ag), antibody to hepatitis B core antigen (anti-HBc), or antibody to hepatitis B surface antigen (anti-HBs). After randomization, 20 patients were given 20 μg and 19 patients received 40 μg of vaccine in a four-dose regimen of HBV immunization. Immune response was assessed by measuring anti-HBs at the 2nd, 6th, 7th and 12th months. Anti-HBs at levels equal to or more than 10 IU/L were considered to constitute seroconversion.*

Results: *Rates of seroconversion in the 20 μg versus the 40 μg groups at the 2nd, 6th, 7th, 12th month were 50.0%:52.6% (p = 0.869), 65.0%:100.0% (p = 0.004), 95.0%:100.0% (p = 0.323) and 80.0%:100.0% (p = 0.040) respectively. Six months after completing the vaccination, some patients (20.0%) in the 20 μg group had lost their immune response while all in the 40 μg group still maintained their seroconversion. During the study, there was no significant change in eGFR in the two groups (p>0.05), and minor adverse effects including local pain, malaise, fatigue, and dizziness were not significantly different between the two groups.*

Conclusion: *Seroconversion rates of the two groups were not significantly different after completion of HBV vaccination, but only patients in the group receiving the double dose were able to maintain seroconversion 6 months later. The proper hepatitis B vaccination for patients with CKD stage 3 with negative makers of HBV should be immunization with a four-dose regimen using 40 μg of vaccine.*

Keywords: *hepatitis B virus vaccination, CKD patients, seroconversion*

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At present, hepatitis B virus (HBV) infection is estimated to affect many millions of people worldwide[1], and it is an important blood-borne infection. Patients with chronic kidney disease (CKD) requiring renal replacement therapy (RRT), especially hemodialysis (HD), are at high risk of HBV infection and being carriers capable of spreading HBV to HD staff and other patients[2,3]. Progression of CKD to end-stage renal disease (ESRD) adversely affects the patient's immune response, and this may increase the risk of severe HBV infection with raised morbidity and mortality. Thus the prevention of HBV infection is important for kidney disease patients worldwide.

HBV infection can be prevented by vaccination. In 1999, it was reported from the USA that the risk of HBV infection was 70% lower in vaccinated HD patients than in those unimmunized[4]. However immune response to vaccination in patients with CKD requiring RRT has been unsatisfactory. The impaired response to HBV vaccines in dialysis patients has been attributed to inadequate dialysis, anemia, poor nutritional status, obesity, genetic factors, smoking, and immunosuppressive medication[5]. Testing of immune response should measure the concentration of antibody to hepatitis B surface (Anti-HBs) 1 month

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after the administration of the last dose of hepatitis B vaccine. An increase in anti-HBs concentration from baseline (<10 IU/L or negative) to protective level (≥10 IU/L) is considered as seroconversion that is likely to prevent HBV infection. Seroconversion rates in response to hepatitis B vaccine in the HD population are only 40-70% compared to more than 95% in the general population[6,7]. Although lower hepatitis B vaccine responsiveness has been widely recognized in the ESRD population, to what extent moderate to advanced CKD modifies vaccine responsiveness remains unclear. There has been a small number of studies that examined vaccination in the setting of CKD, and most of these showed that patients with higher estimated glomerular filtration rates (eGFR) had a better chance of achieving and sustaining immunity[8]. At present, based on currently available evidence and experience, experts agree on the recommendation of hepatitis B vaccination before dialysis commencement. The Kidney Disease Improving Global Outcomes (KDIGO) 2012 also recommends that all adults who are at high risk of progression of CKD and have eGFR of less than 30 ml/min/1.73 m^2 be immunized against hepatitis B. Early vaccination maximizes the chance of achieving and sustaining immunity[9].

The CDC 2012[9] recommends that HD patients, like other immunosuppressed ones, should be given 4 doses of recombinant DNA hepatitis B vaccine of 40 μg intramuscularly at 0, 1, 2, and 6 months, but the ideal regimen of vaccination for non-dialyzed patients remains unclear. There is also uncertainty about the benefits of the double dose hepatitis B vaccine in CKD.

In a study at Chulalongkorn University, Thailand in 2000, Wanida Somboonsilp[10] compared seroconversion after hepatitis B vaccination using a lower dose (10 μg) intradermal vaccination and double standard dose (40 μg) intramuscular vaccination in predialytic chronic renal failure (CRF) patients. The study found that giving a 4-dose regimen of hepatitis B vaccine of 40 μg induced immune response in 90% of predialytic CRF patients. However, this study did not classify patients according to GFR as recommended by current guidelines, and patients were in late stage CKD with mean serum creatinine of 4.6 mg/dL. There are as yet no hepatitis B vaccination guideline for patients with CKD stage 3 and 4.

In 2010, Siddiqui S[11] studied the immune response to hepatitis B vaccination of CKD patients using a modified schedule of 20 and 40 μg of vaccine. This study showed that the immune response rates after 4 doses of 40 μg of hepatitis B vaccine were likely to be greater than those after 20 μg, but for mild and moderate groups of CKD patients, the immune response rates of the 20 and 40 μg groups were not different. The question of whether 40 μg of hepatitis B vaccine induces significantly greater immune response than 20 μg in mild and moderate groups of CKD patients remains to be clarified. The objective of this study was to compare the seroconversion rates of patients with CKD stage 3 who received 4 doses of 20 μg intramuscular hepatitis B vaccine with those of patients receiving 40 μg.

Material and Method

This research was approved by the ethical committee of Rajavithi Hospital (056/2557) on May 14th, 2014. This study was a prospective randomized controlled trial designed to compare seroconversion in CKD stage 3 patients who received hepatitis B vaccination intramuscularly in a 4-dose regimen of 20 μg at 0, 1, 2, and 6 months with that of patients receiving 40 μg vaccine. Fig 1 shows the study design.

Study population

This study involved all patients with CKD stage 3 receiving care at the renal out-patient department of Rajavithi Hospital between May 2014 and December 2015. Inclusion criteria were patients with CKD stage 3 who had estimated glomerular filtration rate (eGFR) measured by CKD-EPI of 30-59 ml/min/1.73 m^2, stable kidney function (change of eGFR <10% during the 3 months prior to the study), and who were aged ≥18 years. Exclusion criteria were: patients with evidence of HBV infection (positive results of hepatitis B surface antigen (HBs Ag), antibody to hepatitis B core (anti-HBc) and antibody to hepatitis B surface (anti-HBs)); history of HBV vaccination; autoimmune disease; immunodeficiency disease; malignancies; pregnant women; patients receiving immunosuppressive medication; and patients with cirrhosis or abnormal liver function test, HbA1c >8%, serum albumin <3.5 g/dL, hemoglobin <10 g/dL or body mass index (BMI) ≥35 kg/m^2.

After these patients without HBV infection (negative for HBs Ag, anti-HBs, and anti-HBc) had signed an informed consent, their medical history, physical examination and laboratory results were evaluated by a nephrologist. Subjects participating in the study were randomized into 2 groups by permuted-block randomization with varying block sizes. Those in the first group (20 μg group) received hepatitis B

vaccine of 20 µg intramuscularly at the deltoid muscle with 4 doses at 0, 1, 2, and 6 months. Patients in the second group (40 µg group) received hepatitis B vaccine of 40 µg intramuscularly, 20 µg in each deltoid, also with 4 doses at 0, 1, 2, and 6 months. The hepatitis B vaccine was Engerix™-B (20 µg/mL doses), a recombinant DNA hepatitis B vaccine manufactured by GlaxoSmithKline Biologicals SA, Belgium and approved by the Food and Drug Administration of Thailand. Blood concentration of HBs Ag, anti-HBs, and anti-HBc were determined by electrochemilumines cence immunoassay (ECLIA) using a Cobas® e 601 immunoassay analyzer (Roche Diagnostics, Japan).

Anti-HBs response was measured at the 2nd, 6th, 7th and 12th months i.e. at 1 month after the 2nd, 4 months after the 3rd, and 1 and 6 months after the 4th doses. An anti-HBs concentration of ≥10 IU/L was considered a marker of seroconversion. Then we compared seroconversion rates of the 20 µg group with that of the 40 µg group at the 2nd, 6th, 7th and 12th months.

Statistical analysis

Data analysis was performed using SPSS software version 16.0 ((SPSS Inc., Chicago, Illinois, USA). Continuous data of baseline characteristics were presented as mean ± SD and categorical data as number with percentage. We used independent sample t-test to compare numerical data with normal distribution, and we used Chi-square test to compare categorical data. A *p*-value of less than 0.05 was considered statistically significant.

Results

Fig. 2 shows a summary of enrollment randomization and follow-up of the study participants. A total of 163 patients with CKD stage 3 were screened for HBV protocol including HBs Ag, anti-HBs, and anti-HBc, and 115 were excluded due to evidence of previous HBV infection or immunization: positive anti-HBc, n = 23, positive of anti-HBs, n = 88, and positive HBs Ag, n = 4. Nine patients were lost to follow-up before randomization, and therefore. Finally 39 patients were included into this study. Their age ranged from 28 to 83 years with mean age 64.6±13.4 years, 35.9% were males, 64.1% were females, and 61.5% were diabetic patients. Mean BMI and eGFR were 27.7±5.4 kg/m^2 and 46.5±8.7 ml/min/1.73 m^2 respectively. Hemoglobin, serum albumin and fasting blood sugar were 12.1±1.8 g/dL, 4.4±0.4 g/dL and 119.7±22.5 mg/dL respectively.

Patients were randomized into 2 groups: 20

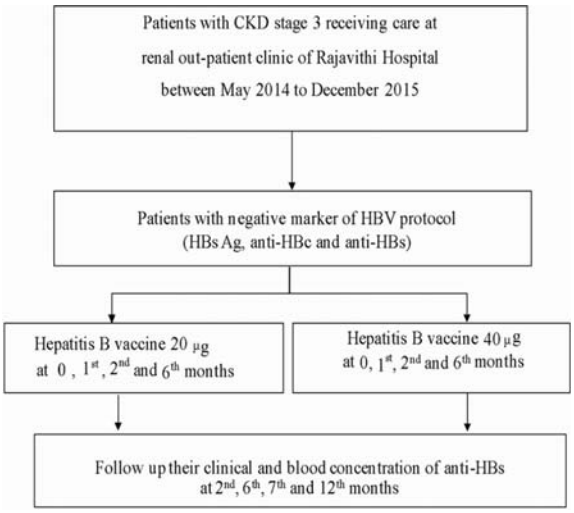

Fig. 1 Study procedure.

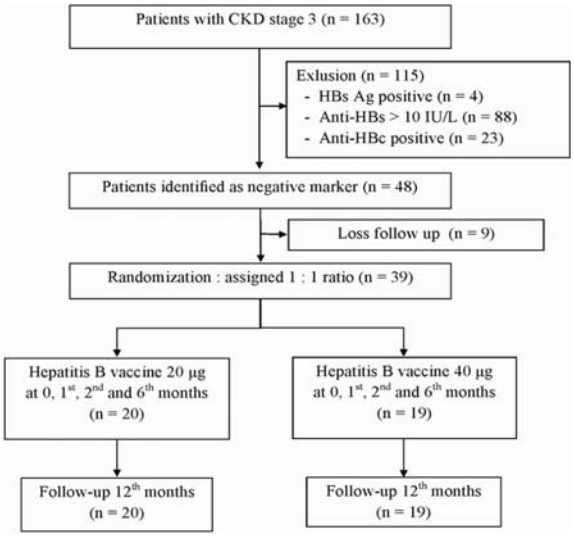

Fig. 2 Enrollment, randomization, and follow-up of the study participants.

for doses of 20 µg, and 19 for 40 µg doses. Baseline characteristics of the two groups were not significantly different in any variable (Table 1). Both groups were given 4 doses of hepatitis B vaccine at 0, 1, 2, and 6 months intramuscularly. Immune response was evaluated by blood concentration of anti-HBs at the 2nd month (1 month after 2nd dose), the 6th month (4 months after 3nd dose), the 7th month (1 month after 4nd dose) and the 12th month (6 months after having completed all 4 doses). Anti-HBs concentration of ≥10 IU/L was defined as seroconversion. Sero-conversion rates at the 2nd, 6th, 7th and 12th month were

51.3%, 82.1%, 97.4% and 89.7% respectively. Table 2 shows the seroconversion rates of each group.

Both groups had increasing rates of seroconversion, although the 20 μg group showed a slower rate of seroconversion compared to the 40 μg group. At the 6th month, the first group had significantly lower seroconversion than the second group (65.0% and 100%, $p = 0.004$). At the 7th month (after having completed all 4 doses of vaccination), seroconversion of patients in the first group was not significantly different from that of the second group (95.0%:100.0%, $p = 0.323$). At the 12nd month (6 month after completely vaccination), however, patients in the first group had significantly lower seroconversion than those in the second group (80.0%: 100.0%, $p = 0.040$) with some patients in the first group having lost immune response (anti-HBs concentration <10 IU/L) whereas all patients in the second group had retained seroconversion. The seroconversion rates of the two groups were not different during the vaccination period, but the second group maintained significantly longer seoconversion after vaccination than the first group.

During the study, there was no significant change in eGFR in the two groups ($p>0.05$). At the start of the study, eGFR of the first and second groups were 44.4±8.7 and 48.7±8.3 ml/min/1.73m^2 respectively. At the 12nd month, they were 43.9±9.4 and 47.8±7.4 ml/min/1.73 m^2, respectively.

There were only minor adverse effects from the vaccination including local pain for 1-2 days (74.3%), fatigue/malaise (12.8%), and dizziness (7.7%). The adverse effects were not significantly different in the two groups (Table 3).

Discussion

Progression of CKD may adversely affect host immune response, making patients prone to infection, which is the most common cause of death in CKD patients. Severity of immune abnormalities increases with deterioration of renal function. The main factor of immune dysfunction in these patients is uremia. Hypercytokinemia, a typical feature of uremia, is probably due to accumulation of pro-inflammatory cytokines as a consequence of decreased renal elimination and/or increased generation induced by uremic toxins, oxidative stress, volume overload, or other comorbidities. On the other hand, uremia is associated with immunosupression[12], and the function of polymorphonuclear white blood cells, lymphocytes and monocytes is altered in uremic patients, resulting

Table 1. Baseline characteristics of study population

Characteristics	HBV Vaccination regimen	*p*-value
	20 μg (n = 20)	40 μg (n = 19)	
Age (year)	64.8±15.6	64.4±11.2	0.922
Male (n, %)	7 (35)	7 (36.8)	0.905
Diabetes (n, %)	15 (75)	9 (47.4)	0.076
BMI (kg/m^2)	28.6±6.3	26.7±4.2	0.302
eGFR (ml/min/1.73m^2)	44.4±8.7	48.7±8.3	0.127
Hemoglobin (g/dL)	11.9±2.0	12.3±1.5	0.529
Serum albumin (g/dL)	4.3±0.3	4.5±0.4	0.242
Fast blood sugar (mg/dL)	122.5±23.7	116.9±21.4	0.448

Values are represented as n(%) and Mean±SD.

Table 2. Relationship between vaccine regimens and seroconversion rates after HBV vaccination

Seroconversion	HBV Vaccination	*p*-value
20 μg (n = 20)	40 μg (n = 19)	
2nd month	10 (50.0)	10 (52.6)	0.869
6th month	13 (65.0)	19 (100.0)	0.004*
7th month	19 (95.0)	19 (100.0)	0.323
12th month	16 (80.0)	19 (100.0)	0.040*

Values are represented as n(%)
* = Significant at $p<0.05$

Table. 3 Adverse effects after vaccination

	Adverse effects 20 µg (n = 20)	HBV vaccination 40 µg (n = 19)	*p*-value
Local pain	1 (5.0)	4 (21.1)	0.134
Fatigue/malaise	1 (5.0)	1 (5.3)	0.970
dizziness	2 (10.0)	1 (5.3)	0.579

Values are represented as n (%)

in an impaired host response to infection or vaccination[13].

HBV infection is a major chronic complication in patients receiving long-term HD. Chronic HBV infection may lead to cirrhosis or hepatocellular carcinoma. Treatment of HBV infection is complicated and expensive. Thus, prevention by hepatitis B vaccination is the goal of clinical care for patients without HBV infection (negative for HBsAg, anti-HBs, and anti-HBc). However, immune response after hepatitis B vaccination is lower in CKD patients compared to patients without kidney diseases. Lower responsiveness to hepatitis B vaccination occurs despite using higher vaccine doses in HD patients than in the general population. Immune response rates in HD patients are only 40-70% compared to more than 95%[1] in healthy populations; therefore, hepatitis B vaccination is recommended for patients with CKD prior to dialysis commencement. Early hepatitis B vaccination maximizes the chance of achieving and sustaining immunity[8]; however, no guidelines for hepatitis B vaccination for CKD patients have been issued yet. In previous studies, 40 µg of hepatitis B vaccination has been found to induce significantly greater immune response than 20 µg in ESRD patients, but for patients with earlier stages of CKD including CKD stage 3, who commonly first present for treatment at renal clinics, it is not clear whether a high-dose regime would induce a better immunity than the conventional dose.

This was the first study to evaluate immunization with hepatitis B vaccination in patients with CKD stage 3. Seroconversion after intramuscular hepatitis B vaccination was compared in patients receiving a 4-dose regimen of 20 µg and those who were given 40 µg. The low-dose group showed their best conversion at 7th months (or 1 month after the 3rd dose) at 95%, whereas the high-dose group still had 100% (95.0%: 100.0%, p = 0.323). At the end of the study (12th months) 80% of the low dose had maintained their seroconversion compared to all of the high-dose group (80.0%: 100.0%, p = 0.040). CKD patients who are susceptible to hepatitis B infection or need to induce rapid protection should use the 4-dose regimen of 40 µg hepatitis B vaccine because, in this study, the high-dose group had more rapid immune response than the low-dose one. After vaccination was complete, the seroconversion rates of the two groups were not significantly different, but only the second group maintained seroconversion for the following 6 months. These findings suggest that hepatitis B vaccination for patient with CKD stage 3 should be 4 dose regimen of 40 µg vaccine. A further period of follow-up will show how long the serocenversion of this regime is maintained. We are continuing our study, and in time will be able to report this interesting outcome.

Thailand is an endemic area of hepatitis B infection with high chronic carrier state. At the beginning of our study out of 163 patients who were screened for hepatitis B protocol (HBsAg, anti-HBs, and anti-HBc), only 48 patients were free of all markers of HBV, a prevalence of approximately 70.6%, which corresponds with the results of the study of Wanida Somboonsilp[10] in which it was 71%. CKD stage 3 in Thailand affects approximately 3.75 million people[14], and the 30% of these patients who are still are negative of HBV markers should be immunized as soon as possible before the disease progresses to HD and kidney transplant. We recommend that a National policy on hepatitis B vaccination for patients with CKD stage 3 should be developed in line with our study using a 4-dose regimen of 40-µg vaccine in all patients with negative makers of HBV.

Limitations of this study were its relatively small sample size and its short duration. Screening of chronic kidney disease for HBV infection should be routine. A study of longer duration should further evaluate the effectiveness of both regimens, and this is already in progress.

Conclusion

After completion of HBV vaccination in

patients with CKD stage 3, the high-dose group showed a tendency to have more seroconversion than the low-dose group, but the differences we are not statistically significant. However, 6 months after completion of HBV vaccination, the high-dose group had maintained significantly more seroconversion than the lower-dose group. The proper hepatitis B vaccination for patients with CKD stage 3 with negative markers of HBV should be a four-dose regimen of of 40 μg vaccine.

What is already known on this topic?

For CKD stage 5 or dialysis patients, a guideline already exists recommending a four-dose regimen of 40 μg hepatitis B vaccine; however, no hepatitis B guidelines have yet been issued for patients with CKD stages 3 and 4.

What this study adds?

The proper hepatitis B vaccination for patients with CKD stage 3 should be a four-dose regimen of 40 μg of vaccine to maintain seroconversion for 12 months.

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Potential conflicts of interest

None.

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การศึกษาแบบสุ่มที่มีการควบคุมในการเกิดภูมิคุ้มกันหลังได้รับวัคซีนป้องกันไวรัสตับอักเสบ บี โดยการฉีดเข้ากล้ามเนื้อระหว่างขนาด 20 ไมโครกรัม เปรียบเทียบกับ 40 ไมโครกรัม ในผู้ป่วยโรคไตเรื้อรังระยะที่ 3

อุดม ไกรฤทธิชัย, เศรษฐพร เศรษฐการุณย์

ภูมิหลัง: *การให้วัคซีนป้องกันไวรัสตับอักเสบ บี แก่ผู้ป่วยโรคไตเรื้อรังยังไม่มีแนวทางที่ชัดเจน และยังไม่มีหลักฐานที่แสดงถึงประสิทธิภาพของการให้วัคซีน 40 ไมโครกรัมว่าสามารถกระตุ้นการเกิดภูมิคุ้มกันได้เหนือกว่าวัคซีน 20 ไมโครกรัม*

วัตถุประสงค์: *เพื่อเปรียบเทียบการเกิดการเกิดภูมิคุ้มกันหลังการให้วัคซีนป้องกันไวรัสตับอักเสบ บี ชนิด recombinant DNA โดยการฉีดเข้ากล้ามเนื้อจำนวน 4 ครั้ง (0, 1, 2, 6 เดือน) ระหว่างการให้วัคซีน 20 ไมโครกรัมและ 40 ไมโครกรัม*

วัสดุและวิธีการ: *ผู้ป่วยโรคไตเรื้อรังระยะที่ 3 ที่ไม่เคยติดเชื้อไวรัสตับอักเสบ บี หรือได้รับวัคซีนป้องกันโรคมาก่อน รวมทั้งมีผลตรวจคัดกรองไวรัสตับอักเสบ บี (HBs Ag, anti-HBs, anti-HBc) เป็นลบจำนวน 39 คนถูกสุ่มแบ่งเป็น 2 กลุ่ม กลุ่มที่ 1 จำนวน 20 คน ได้รับวัคซีนขนาด 20 ไมโครกรัม จำนวน 4 ครั้ง และกลุ่มที่ 2 จำนวน 19 คน ได้รับวัคซีน 40 ไมโครกรัม จำนวน 4 ครั้ง ติดตามการเกิดภูมิคุ้มกันโดยการเจาะเลือดตรวจระดับ anti-HBs ที่ 2, 6, 7 และ 12 เดือน โดยกำหนดว่าระดับ anti-HBs มากกว่าหรือเท่ากับ 10 IU/L เป็นระดับที่เกิดภูมิคุ้มกัน*

ผลการศึกษา: *อัตราการเกิดภูมิคุ้มกันในกลุ่ม 20 และ 40 ไมโครกรัมในเดือนที่ 2, 6, 7 และ 12 เท่ากับ 50.0%: 52.6% (p = 0.869), 65.0%: 100.0% (p = 0.004), 95.0%: 100.0% (p = 0.323) และ 80.0%: 100.0% (p = 0.040) ตามลำดับ เมื่อติดตามไปหกเดือนภายหลังฉีดวัคซีนครบ พบว่า 20.0% ของผู้ป่วยในกลุ่ม 20 ไมโครกรัมจะสูญเสียภูมิคุ้มกัน ขณะที่กลุ่ม 40 ไมโครกรัมยังคงมีภูมิคุ้มกันทุกคน การเปลี่ยนแปลงของ eGFR ไม่แตกต่างทั้งสองกลุ่ม (p>0.05) อาการข้างเคียงที่เกิดจากการได้รับวัคซีน ได้แก่ อาการปวดเฉพาะบริเวณฉีดยา, ปวดกล้ามเนื้อ, อ่อนเพลียและวิงเวียนศีรษะในทั้ง 2 กลุ่มไม่แตกต่างกัน*

สรุป: *ภายหลังการฉีดวัคซีนป้องกันไวรัสตับอักเสบ บี ทั้งสองพบว่าการเกิดภูมิคุ้มกันกลุ่มไม่แตกต่างกันแต่กลุ่ม 40 ไมโครกรัมทุกคนยังคงมีภูมิคุ้มกันทุกคนต่อเนื่องไปหกเดือนหลังฉีดวัคซีนครบ ดังนั้นผู้ป่วยโรคไตเรื้อรังระยะที่ 3 ที่มีผลตรวจคัดกรองไวรัสตับอักเสบ บี เป็นลบควรฉีดวัคซีน 40 ไมโครกรัมจำนวน 4 ครั้ง*