Low-Dose Intradermal and Subcutaneous Versus Intramuscular Hepatitis B Vaccination in Primary Non-Responding Hemodialysis Patients

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Objective: *Patients with end-stage renal failure are at high risk of hepatitis B virus (HBV) infection. They have impaired immune response to HBV intramuscular (i.m.) vaccine. Non-response (anti HBs titer < 100mIU/ml) hemodialysis patients (HD) with the previous three-dose i.m. vaccination were examined with booster dose vaccine by i.m. , intradermal (i.d.) and subcutaneous (s.c.) routes.*
Material and Method: *Thirty-four HD patients who had been vaccinated with three-dose vaccine (40 microgram, 2 ml, Engerix B, i.m.) and had anti-HBs titer less than 100mIU/ml were selected. They were randomly divided into three groups and received a fourth dose of vaccine by i.m. (40 microgram, 2 ml), i.d. (10 microgram.0.5 ml) and s.c. (10 microgram, 0.5 ml). Then, serum anti-HBs titer was determined after 45 days and 6 months.*
Results: *Forty five days after completion of the re-vaccination course, anti-HBs titer was above 100 mIU/ml in 6/11, 3/11 and 4/12 of i.m. s.c. and i.d. groups, respectively ($p > 0.05$). After six months, 4/11,3/11 and 2/12 of patients had anti-HBs titer above 100mIU/ml ($p > 0.05$).*
Conclusion: *With lower dose of vaccine (10 microgram) in s.c. groups, these patients had lower change in their anti-HBs titer. Therefore, it is cost effective and practical to offer other vaccination schemes.*

Keywords: *hepatitis B vaccination, hemodialysis patients, re-vaccination, Non-responder*

J Med Assoc Thai 2006; 89 (10): 1648-53
Full text. e-Journal: *http://www.medassocthai.org/journal*

Chronic hepatitis B virus (HBV) infection is one of the most important public health problems in Asia and to most developing countries. Over 350 million people are suffering from chronic HBV infection in the world[1,2].

Chronic liver disease caused by HBV has been considered as an important problem in dialysis units since 1960 and surveillance of hemodialysis (HD) associated hepatitis was recommended by the Centers for Disease Control and Prevention (CDC) since 1970[3].

A higher rate of HBV infection was reported when less than 50% of the patients had been vaccinated[4]. The CDC guideline for prevention of HBV infection call for all HD patients and staff to be vaccinated. After we followed this guideline, the prevalence and incidence of HBV infections in HD patients have dropped significantly over the past 2 decades[3,5].

Patients with chronic renal failure (CRF) have impaired immune system[6,7] and the response to HBV vaccine is much lower in comparison to healthy people[8-10]. Monocyte dysfunction and under expression of the TCR/CD3 antigen receptor by Th-1 cells have been reported for that[11,12]; therefore, the response of the antibody forming cells would be impaired or absent.

For these reasons, some recent studies recommended different strategies in non-responsive CRF patients such as: multiple intramuscular injections (i.m.)[13], double dose injections[14,15], conjugated HBV

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vaccine with interleukin 2[16,17], intradermal (i.d.), or subcutaneous (s.c.) injections[18-20].

Anti-HBs level above 10 mIU/ml is protective, but some studies have suggested an antibody higher than 100 mIU/ml may be necessary to guarantee a more adequate protection[21-23,25].

Among these protocols of vaccinations, it seems that repeated s.c. or i.d. injections are more effective than i.m. injection. However, the amount of vaccine in the i.d. and s.c. injection is lower than in i.m, which is more cost-effective.

The objective of this prospective and randomized study was to compare the adequate antibody response (> 100mIU/ml) to s.c. and i.d. HBV vaccine with i.m. injections in HD patients with an anti HBs titer of less than 100mIU/ml.

Material and Method

This study was performed on all hemodialysis patients who referred to the Department of hemodialyisis of Shahid Beheshti hospital in Babol city since November 2003.This department serves all HD patients, living in Babol and the villages around it. All HD patients with HBs Ag and anti-HBc positive, and patients with abnormal aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were excluded. Until November 2003, HBV vaccinations of all patients were completed with three doses (40microgram, 2 ml) of Engerix-B vaccine (Heberbiovac HB, Cuba) intramuscularly in deltoid muscle (at 0, 1 and 6 month). HBs-Ab (anti-HBs) titer was determined using enzyme linked immune assay (ELISA) method and all patients (34 patients) with antibody levels less than 100mIU/ml were selected.

These patients were randomly divided into three groups and given the fourth dose of vaccine.

Eleven patients received the next dose of Engrix-B vaccine (40 microgram, 2 ml) intramuscularly (i.m. group), 11 patients (10 microgram 0.5 mL) intradermaly (i.d. group) and 12 patients (10 microgram, 0.5 ml) subcutaneously (s.c. group). Forty five days and 6 months after the last dose of vaccine, HBsAb (anti-HBs) titer was tested by ELISA method (Rondox, England).

AST and ALT enzymes in all patients were measured and no changes were noticed in the results. The local ethics committee approved the study and informed consent was obtained from all patients.

Data was analyzed statistically by SPSS, version 10. Chi-square, t-student and Fisher exact test were used to compare the antibody levels regarding response. $p < 0.05$ was considered significant.

Results

In this study, 34 patients (22 females and 12 males) were evaluated. The mean age and the sex ratio of the patients in each group have been shown in Table 1.

There was no significant difference between patients in three groups regarding sex and mean age ($p > 0.05$).

Forty five days after the completion of the revaccination course, mean level of anti-HBs titer in i.m., s.c. and i.d. groups were 132 ± 97, 74 ± 86.6 and 80.15 ± 82.5, respectively ($p > 0.05$). The HBs titer after 6 month has been showed in table II ($p > 0.05$).

Forty five days after completion of revaccination course, the number of patients in i.m. group with anti-HBs titer above 100mIU/ml were more than s.c. and i.d. groups (6/11 vs 3/11 and 4/12, respectively), but there was no significant difference ($p > 0.05$).

Six months after completion of the vaccination course, anti-HBs titer was above 100mIU/ml in 4/11, 3/11 and 2/12 in i.m., s.c., and i.d. group respectively (Table 2).

During the study, no complications with vaccination such as erythema, severe pain (except in i.d. group) or infection at the site of injection, was noticed and there was no clinical HBV infection in these patients.

Table 1. Demographic characteristics of hemodialysis patients in the study

	Intramuscular	Intradermal	Subcutaneous
No of patients	11	12	11
Sex (M/F)	3/8	5/7	4/7
Mean age (year)	53.73 ± 19.76	59.58 ± 21.13	60.30 ± 21.08
$p > 0.05$			

Table 2. Adequate response, mean and GMT anti-HBs titer 1.5 and 6 month of the completion vaccine in each group

Vaccination	1.5 months			6 months			Total
	>100mIU/ml	<100mIU/ml	Mean (GMT)	>100mIU/ml	<100mIU/ml	Mean (GMT)	
Intramuscular	6	5	132±97 (73.78)	4	7	104±87 (24.86)	11
Subcutaneous	8	3	74±86.6 (35.73)	3	8	83.8±65 (19)	11
Intradermal	8	4	80.15±82.5 (40.94)	2	10	40.9±66 (13.81)	12
$p > 0.05$							

Discussion

The risk of HBV infection is higher in hemodialysis patients. CDC reported five outbreaks of HBV infection in such patients in the USA (1994)[26]. Recombinant HBV vaccine has been recommended for all patients in HD units since 1980. However, unfortunately the success rate of vaccination is lower than in the general population[8,10,27]. Several authors reported i.d. route of injection (instead of i.m. method) in healthy individuals with a good safety and more immunogenicity[28,29].

The i.d. or s.c. route of HBV re-vaccination has been reported by several authors in HD patients[30-33]. Some of these studies were performed on HD patients who had not responded to previous vaccination using i.m. route[19,30,32], others started the vaccination using i.d. or s.c. routes in patients who had not been vaccinated before[20,26,34].

Many of the procedures were set up to increase anti-HBs titer above 10mIU/ml (protective response) but some tried to increase its level to greater than 100 mIU/ml (Adequate response)[23-25].

In this study, our optimal anti-HBs titer in HD patients was above 100mIU/ml (Adequate response). Therefore, patients who had been vaccinated by three doses of i.m. injections and had anti-HBs titer less than 100 mIU/ml were selected, and re-vaccinated by i.m., s.c. or i.d. routes of injection.

After 1.5 month, the number of patients with adequate response to booster dose of vaccine in i.m. group was more than s.c. and i.d. groups (6/11 vs 3/11 and 4/2) respectively, although the difference was not statistically significant.

Six months after the last dose of vaccine (booster dose), anti-HBs titer remained higher than 100 mIU/ml in three patients of s.c. group, but four and three patients in the i.m. and i.d. groups, respectively. Therefore, the number of patients with adequate response did not change in s.c. group after 6 months.

Fabrizi et al injected the fourth dose of vaccine by id route in HD patients who have not previously responded to HBV vaccine by i.m. route and reported seroprotection (titer > 10 mIU/ml) after 3 months in almost all of them, although in comparison with i.m. injected individuals, there was no statistical difference. On the other hand, the median levels of anti-HBs titer in responder patients in i.d. group were significantly higher than those of i.m. group. However, after six months, he could not show any significant difference between i.d. and i.m. regarding to response[30].

Vlorssopoulos et al showed i.d. administration of HBV vaccine, to be effective in repeated small injections to be effective (anti-HBs titer $\geq$ 10 mIU/ml) for at least 6 months[31].

Propst et al evaluated antibody response to HBV vaccination in 81 HD patients by i.m., s.c. and i.d. routes. He showed that intradermal HBV vaccination response with a higher dose (20 microgram) than previously used in HD patients is higher comparing to conventional i.m. dose and s.c. method-vaccination[20].

In this study, mean levels of anti-HBs titer were decreased in all groups after 6 months. The p-value for s.c. group was 0.207, which was not significant (p-value for i.m. and i.d. groups were 0.041 and 0.044, respectively). In fact, the change of anti-HBs titer in s.c. group was slower than other groups and it may cause a longer protection for HD patients.

In conclusion, the intradermal route of HBV vaccination maybe less practical compared to i.m. and s.c. We need a higher dose of vaccine (40 microgram, 2 ml) in i.m. route that its cost-effectiveness must be considered. While, CDC reported suboptimal response to HBV vaccine by s.c. route[35], in this study, the authors used 10 microgram of vaccine and these patients had slower change in their anti-HBs titer in comparison to other routes. So, further studies maybe needed for re-evaluation of s.c. vaccination for HBV in HD patients.

Acknowledgement

The authors would like to thanks to all personnel of HD Unit of Shahid Beheshti Hospital, Dr.Firousjahi and Mr.M.R.Bozorgi and excellent assistance.

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การฉีดวัคซีนตับอักเสบบีขนาดต่ำเข้าชั้นผิวหนัง หรือใต้ผิวหนังหรือเข้ากล้ามเนื้อซ้ำในผู้ป่วยฟอกไตที่ไม่ตอบสนองต่อการฉีดเข้ากล้ามเนื้อ

ฮาดี ซอร์ซีม, โมฮะหวัด เรซา เอสเมไล ดูกี, มีนา ซาดัด เอบราฮิมเนจาด

วัตถุประสงค์: *เพื่อทำการศึกษาในผู้ป่วยไตวายระยะสุดท้ายที่ไม่ได้ผลต่อการฉีดวัคซีนตับอักเสบบีแบบเข้ากล้ามเนื้อเพิ่มเติมอีกด้วยการฉีดวัคซีนซ้ำ เข้ากล้ามเนื้อ หรือ เข้าชั้นผิวหนัง หรือ เข้าใต้ผิวหนัง*

วัสดุและวิธีการ: *ศึกษาในผู้ป่วยดังกล่าว 30 คน โดยแบ่งผู้ป่วยออกเป็น 3 กลุ่ม โดยฉีดวัคซีนซ้ำเป็นครั้งที่ 4 ในขนาด 40 ไมโครกรัมเข้ากล้ามเนื้อ 10 ไมโครกรัมเข้าชั้นผิวหนัง หรือ 10 ไมโครกรัมเข้าใต้ผิวหนัง ต่อมาได้ตรวจระดับแอนติ-เอช-บี-เอส ซ้ำในวันที่ 45 และ 180*

ผลการศึกษา: *วันที่ 45 พบระดับ แอนติ-เอช-บี-เอส สูงกว่า 100 mIU/มล. ในผู้ป่วย 6 รายใน 11 ราย ชนิดฉีดเข้ากล้ามเนื้อ, 3 ใน 11 ราย ชนิดฉีดเข้าใต้ผิวหนังและ 4 รายใน 12 รายชนิดฉีดเข้าชั้นผิวหนัง ($p > 0.05$) ในวันที่ 180 พบว่า 4 รายใน 11 ราย (กล้ามเนื้อ), 3 ราย ใน 11 ราย (ใต้ผิวหนัง) และ 2 รายใน 12 ราย (เข้าชั้นผิวหนัง) ก็ได้ผลแอนติ-เอช-บี-เอส สูงกว่า 100 mIU/มล. ($p > 0.05$)*

สรุป: *การฉีดวัคซีนตับอักเสบบีแก่ผู้ป่วยไตวายระยะสุดท้ายโดยให้เข้าใต้ผิวหนัง ได้ผลต่ำกว่าวิธีอื่น ๆ*