

Efficacy of Hepatitis B Virus Vaccination and Antibody Response to Reactivation Dose Among Adult Non-Responders to Primary Hepatitis B Vaccination in Chronic Hepatitis C Egyptian Patients

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ABSTRACT

BACKGROUND AND AIMS: Acute HBV infection in patients with chronic HCV-related liver disease is associated with a severe

and often fulminant course of the disease. Additionally, HCV patients may be at a higher than an average risk of acquiring hepatitis B because of the similar routes of transmission of both viruses. HBV infection can be prevented by the administration of a safe and immunogenic vaccine. Insufficient immune response to hepatitis B virus (HBV) vaccine in patients with chronic hepatitis C virus is frequently encountered and anti-HBs levels may persist for a shorter time than among immune competent persons. The purpose of present study was to determine long-term persistence of anti-HBs among Egyptian patients with chronic hepatitis C infection. It also assesses the need and response to a subsequent challenge with vaccine booster doses.

METHODS: 200 individuals were enrolled; (GI) 100 patients suffered from chronic HCV infection and 100 healthy individuals as a control (GII). Both groups were matched in regard to age and sex. Each individual received a standard 3-dose series of HBV vaccine; 20µg recombinant DNA vaccine of HBV(Euvax-B LG Life science, Korea) administered by IM injection into deltoid muscle at 0, 1, 6 months interval. HBs antibody titer was measured after 4 weeks. Suboptimal or Non-responders (anti-HBs titer < 10 IU/L) received a booster dose and reevaluated after 4 weeks; Suboptimal response of group I (42 patients) divided into 2 subgroups: GIa (21 patients), which received 40 µg(double dose) recombinant HBV vaccine and GIb (21 patients), received standard adult dose 20 µg HBV vaccine. 11 individuals with suboptimal response of G II received standard adult dose 20 µg HBV vaccine too.

CONCLUSION: Chronic HCV patients showed lower response rate for standard doses of HBV vaccine especially with advancing age, diabetes and hypoalbuminemia. A double booster dose (40 µg) vaccine would be recommended for them which are better than revaccination with the standard 3 doses recombinant HBV vaccine.

Key words: Chronic HCV patients; HBV vaccine

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INTRODUCTION

Globally, Hepatitis B virus (HBV) and hepatitis C virus (HCV) are two of the most common causes of chronic liver disease and hepatocellular carcinoma (HCC). Both viral infections share common routes of transmission^[1], including parenteral exposure, promiscuous sex and vertical transmission^[2].

Dual infection by HBV and HCV is clearly associated with more severe liver disease than infection by a single virus, whereas acute HBV infection in patients with chronic HCV-related liver disease is associated with a severe and often fulminant course of the disease^[3].

There is convincing evidence suggesting that HBV-HCV co-infection accelerates the liver disease progression and increases the risk of developing HCC^[1].

Patients with chronic HCV have been recommended to receive vaccinations against HBV. The rationale behind these recommendations is based on the fact that HCV patients co-infected with HBV have an increased histological liver damage and a higher risk of HCC. HBV infection can be prevented by the administration of a safe and immunogenic vaccine^[4].

Several studies suggest that the immunogenicity of recombinant HBV vaccine is decreased in patients with chronic HCV, compared to healthy controls, especially in those with advanced liver disease^[5].

The aim of this study is to evaluate the immune response after additional vaccine doses versus doubling dose HBV vaccine in non-responders Egyptian with chronic HCV patients from Damietta.

PATIENTS AND METHODS

This study was carried out on 200 individuals referred to Al-Azhar University Hospital outpatient clinic in one year period. The enrolled individuals were divided into two groups. **Group I:** Included 100 chronic liver disease patients due to HCV infection. **Group II:** Included 100 healthy individuals as a control group.

Both groups were matched in regard to age and sex, vaccinated by 20µg recombinant DNA vaccine of HBV (Euvax-B LG Life science, Korea) administered by intramuscular injection into deltoid muscle at 0, 1, 6 months interval. One month after the third dose of the vaccine HBs antibody titer was measured.

EXCLUSION CRITERIA: (1) Any proved condition that can affect individual's immune response such as: administration of corticosteroids or immunosuppressive drugs, autoimmune diseases, malignancy, unstable thyroid dysfunction and uncontrolled diabetes mellitus. (2) HBsAg and HBeAb seropositivity. (3) Age (< 18 and > 60 years). (4) Any clinical, laboratory or sonographically finding of liver disease for group II.

All cases and controls were submitted to the following

Full history taking, General and local examination for signs of chronic liver disease with exclusion of drug or alcohol abuse, associated chronic cardiac, pulmonary or renal disease.

Pre-vaccination investigations included the following

Complete blood count (CBC) by Automated Cell Counter, aminotransferase level (ALT, AST), alkaline phosphatase, liver function tests (bilirubin, prothrombin time and serum albumin), renal function tests, thyroid function tests, alpha-fetoprotein, fasting blood sugar and HbA1c. HCV Antibody by ELISA third generation. Quantitative Polymerase chain reaction (PCR) for HCV RNA for group I. HBV markers; Detection of HBsAg and HBe-Ab by ELISA test. Anti-Nuclear Antibody titer (by ELISA test). Ultrasonographic studies (using ALOKA SSD-4000 ultrasound scanning system) for evaluation of liver morphologic changes, ascites, splenomegaly and portal hypertension signs in all cases.

Investigations done one month after the three doses of HBV vaccine

Serological tests to measure the level of antibody to hepatitis-B surface antigen (anti-HBs) by ELISA test. The cut-off value for positive HBsAb titer is ≥ 10 IU/L. Individuals with anti-HBs concentration at 10 IU/L or more will be regarded as protected^[6].

Individuals with suboptimal response of both groups (42 HCV patients from group (I) and 11 individuals from control group (II) were given a booster dose. Patients with suboptimal response of group (I) were subdivided into 2 subgroups: GIa (21 patients), who received 40 µg (double dose) recombinant HBV vaccine and GIb (21 patients), received the standard adult dose 20 µg HBV vaccine. Group (II) (11 individuals), received one booster dose 20 µg HBV vaccine.

Anti HBs titer was measured one month later to assess the efficacy of booster dose in different groups. Individuals with anti-HBs concentration at 10 IU/L or more will be regarded as responders.

Statistical analysis

Data was computed with the statistical package for the social science, windows 7 versions, USA (SPSS17 software). Variables with normal distribution were expressed as mean \pm SD. In these variables, the T test was applied for group differences. Non parametric data were expressed as median. The Kalmogorove-Smirnov test was check normal distribution of data. For correlation analysis, spearman's correlation coefficients were calculated with two- tailed P value. The data were considered significant if p value < 0.05^[7].

Ethics

Ethical approval was obtained from the ethics committees of A-Azhar College of Medicine and was in accordance with the 1975 Helsinki Declaration. All subjects provided written informed consent.

RESULTS

Table 1 Demographic data of studied groups.

Parameter		Group I	Group II	P-value
Age (year)	Age (year)	46.98 \pm 7.11	43.44 \pm 7.28	> 0.05
Gender	Male (%)	56 (56 %)	50 (50%)	> 0.05
	Female (%)	44 (44 %)	50 (50%)	
Smoking	smoker	15%	13%	> 0.05
	non smoker	85%	87%	
DM	yes	15%	11%	> 0.05
	No	85%	89%	

Regarding demographic data of the studied groups, there was no statistical difference in all demographic data parameters.

Table 2 Hepatitis B vaccine response in chronic HCV patients VS healthy individuals.

The studied groups	Positive HBsAb titer > 10 mIU/mL (responders)	Negative HBsAb titer < 10 mIU/mL (non-responders)	P-value
Group I (No.=100)	58 (58%)	42(42%)	< 0.05
Group II (No.=100)	89 (89%)	11 (11%)	

The number of patients with protective HBsAb titer is statistically lower in group I compared to group II (58% and 89% respectively and $p < 0.05$).

Table 3 Levels of HBsAb titer among persons with optimal response of both groups.

The studied groups	Range	Mean ± SD	P-value
Patients No. of positive HBsAb individual = 58	10.6-213	117.42 ± 71.07	> 0.05
Control No. of positive HBsAb individuals = 89	10.6-242	103.41 ± 65.12	

No statistical difference in Mean±SD of HBsAb titer in vaccine responders in group I and group II (117.42 and 103.41 respectively $p > 0.05$).

Table 4 Comparison between the HBsAb titer in both groups regarding to DM.

The studied groups	Range	Mean ± SD	P-value	
group I	Diabetic No. = 8	23.00-91.40	50.44 ± 25.24	< 0.01
	Non diabetic No. = 50	10.60-213.00	126.61 ± 70.48	
group II	Diabetic No. = 6	10.6-105.8	47.82 ± 33.42	< 0.01
	Non diabetic No. = 83	11.60-242.00	108.16 ± 65.08	

There is statistical difference in positive HBsAb titer between non diabetic compared to diabetics in both groups.

Table 5 Comparison between positive and negative response in group I as regard HCV viral load.

HCV PCR	+ve response patients No. = 58	-ve response patients No. = 42	P value
RANGE	46000.98 - 1986543.00	28900.65 - 1987632.00	0.05
Mean ± SD	440630.75 ± 4.44	321449.16 ± 3.87	

No statistical differences in group I patients when compared positive response patients with negative response patients according to viremia ($P > 0.05$).

Table 6 Comparison between the mean of HBsAb titer in the group I as regarded to serum albumin.

The studied groups	Range	Mean ± SD	P-value
Patients with +veHBsAB titer and serum Albumin < 3.5. No. = 4	33.90 - 101.90	73.15 ± 30.33	<0.05
Patients with +veHBsAB titer and serum Albumin > 3.5. No. = 54	10.60 - 213.00	120.70 ± 72.26	

Group I shows statistical decrease in +ve HBsAb titer in patients with serum Albumin < 3.5 when compared topatients with +veHBsAb titer and serum Albumin > 3.5 ($P < 0.05$).

Table 7 Effect of a booster dose of HBV vaccine for non-responders.

The studied groups	Positive HBsAb titer > 10 mIU/mL (responders)	Negative HBsAb titer < 10 mIU/mL (non-responders)	P-value
Group Ia (booster dose 40 µg/mL) (No. = 21)	17 (81%)	4 (19%)	< 0.05
Group Ib (booster dose 20 µg/mL)(No. = 21)	9 (43%)	12 (57%)	
Group II non responders (booster dose 20 µg/mL) (No. = 11)	10 (90.9%)	1 (9.1%)	

Comparison between the studied groups (Group Ia, group Ib and group II non responders) regarding the response to HBV vaccine booster dose. The number of patients with positive HBsAb titer > 10 was statistically increased in group Ia compared to group Ib (81% and 43% respectively and $p < 0.05$). Regarding group II (Controls) non-responders, 10 out of 11 individuals (about 90.9%) had positive HBsAb titer after single booster dose (20 µg) HBV vaccine ($p < 0.05$).

Table 8 Level of HBsAb titer after HBV vaccine booster dose of for non-responders.

The studied groups	Range	Mean ± SD	P-value
-ve response Group Ia	1.90 - 9.70	5.95 ± 2.75	> 0.05
-ve response Group Ib	33.90 - 101.90	5.92 ± 2.05	
+ve titer Group Ia	23 - 222	87.58 ± 54.79	< 0.05
+ve titer Group Ib	23.8 - 79.3	56.12 ± 19.62	

Comparison between the mean of efficacy of booster dose single (GIb) and double dose (GIa) HBV vaccine for non-responders.

There is statistical difference in mean of positive HBsAb titer in group Ia as compared to group Ib (87.58 ± 54.79 and 56.12 ± 19.62 respectively, $p < 0.05$). And there was no statistical difference in negative HBs Ab titer.

DISCUSSION

Hepatitis B and hepatitis C are both transmitted through blood-to-blood contact, therefore, it is possible to contract both viruses at the same time or a person with one of the viruses may be infected with the other virus at a later time.

Being infected with both hepatitis B and hepatitis C can lead to severe liver disease including cirrhosis and/or liver failure and increases the risk of developing hepatocellular carcinoma (HCC)^[8].

Hepatitis C virus (HCV) infection is a common cause of chronic liver disease and is the leading indication for liver transplantation. Given the shared risk factors for transmission, co-infection of hepatitis B virus (HBV) with HCV is quite common, and may lead to more significant liver disease^[9].

A recent review by^[10] mentioned that: “Individuals with chronic disease states such as kidney disease, liver disease, diabetes mellitus, as well as those with a genetic predisposition, and those on immunomodulation therapy, have the highest likelihood of non-response. Various strategies have been developed to elicit an immune response in these individuals. These include increased vaccination dose, intradermal administration, alternative adjuvants, alternative routes of administration, co-administration with other vaccines, and other novel therapies”.

As such, HBV vaccine is recommended as the primary means to prevent HBV super-infection and its associated increase in morbidity and mortality in HCV-infected subjects. However, vaccine response (seroconversion with a hepatitis B surface antibody titer > 10 IU/L) in this setting is often blunted, with poor response rates to a standard course of HBV vaccinations in chronically HCV-infected individuals when compared to the healthy populations (40-60% versus 90-95%); this is especially noted in the setting of advanced fibrosis and liver cirrhosis^[11].

Patients with liver cirrhosis had low hepatitis B surface antibody (HBsAb) titers compared to general population. As the age and liver disease progress, the response rate for hepatitis B vaccination still remains to be weaker^[12].

The aim of this study is to evaluate the immune response after additional vaccine doses versus doubling dose HBV vaccine in non-responders Egyptian with chronic HCV patients from Damietta.

We found that positive HBsAb titer was significantly decreased in chronic HCV patients as compared to the control group (58% and 89% respectively and p -value < 0.05). On the other hand the number of patients with negative HBsAb titer was significantly increased in HCV patients as compared to that of normal individuals (42% and 11% respectively p -value < 0.05).

Our results are in agree with^[13] who stated that “Antibody response to HBV vaccination was generally lower in patients with chronic HCV infection compared with controls, indicating some degree of immune compromise in individuals with chronic HCV”.

In a prospective HCV infected cohort, a poor response rate to HBV vaccination as assayed by seroconversion was observed in HCV infected subjects (53%), while a high response rate was observed in healthy or spontaneously HCV-resolved individuals (94%)^[14].

In contrast to these findings, some authors^[15] noticed that HCV patients had excellent response similar to control (89% vs 91% in controls respectively). This may be explained by the high selection of early HCV cases with no fibrosis.

In the current study, there was no statistical difference in the mean of HBsAb titer in group I as compared to control group. These results are similar to those reported by Mattos *et al*^[16].

Insignificant difference was also observed in the response between males and females in both groups (p -value > 0.05). These results are similar to those reported by Wiedmann *et al*^[17] and Mattos *et al*^[16].

There was statistical difference observed in positive HBsAb titer between non diabetic HCV patients compared to diabetics (50.44 ± 25.24 and 126.61 ± 70.48 respectively p -value < 0.01), but there was no statistical difference with negative HBsAb titer, so the response in diabetic patients was lower than non-diabetics. Also there was significant difference in positive HBsAb titer in non-diabetic controls compared to diabetics (47.82 ± 33.42 and 108.16 ± 65.08 respectively p -value < 0.01). This was attributed to the immune compromise state in diabetic patients.

These results are in agreement with Canadian Immunization Guide which stated that “the antibody response is lower in patients with diabetes mellitus (70% to 80%)” (Public Health Agency of Canada)^[18] And also agreed with El-Ghetany *et al*, (2014)^[19].

That is to say diabetics express hypo responsiveness to HBV vaccination and rapid decline of protective anti-HBs compared to healthy ones and a booster dose of HBV vaccine would be recommended.

This work showed that the rate of positive HBsAb titer was significantly increased in patients less than 40 years as compared to that in patients more than 40 years in group I (p -value<0.01). These results are similar to those reported by Wiedmann *et al*^[17] and Mattos *et al*^[16]. So, booster dose of HBV vaccine is recommended for HCV patients over 40years.

In the current study, according to the level of HCV viral load, there was no statistical differences in the response to HBV vaccine in HCV patients when compared positive response patients with negative response patients (p -value>0.05), so viral load has no role in response to vaccine. These results are similar to those reported by Wiedmann *et al*^[17] and Mattos *et al*^[16].

In HCV patients, there was significant decrease in positive HBsAb titer with serum Albumin < 3.5 compared to those patients with serum Albumin > 3.5 (p -value < 0.001). These observations suggest that the vaccine response may be lower in decompensated cirrhotic HCV patients compared to non-cirrhotic, but the small number of cases with low serum albumin limits the value of this finding.

Wiedmann *et al*^[17] and Mattos *et al*^[16] in sub analysis of the HCV cohort found no statistical difference in response to vaccination between patients with or without cirrhosis. But Idilman *et al*^[20] found the difference in vaccine response was restricted to the cirrhotic patients (54% HBV vaccine response vs 72% in non-cirrhotic chronic HCV patients).

Moreover, in a recent study of Roni *et al*^[12] concluded that: “patients with liver cirrhosis had low HBsAb titers compared to general population. As the age and liver disease progress, the response rate for hepatitis B vaccination still remains to be weaker”.

Regarding our observations about efficacy of booster dosing for non-responders in group I (HCV patients), we found that positive

HBsAb titer was statistically higher in group Ia (who received double dose vaccine, 40 µg) when compared to group Ib (who received single dose vaccine, 20 µg) (81% and 43% respectively and p -value < 0.05).

So, double booster dose was more effective than single one. Also, there was significant difference in mean of positive HBsAb titer in those received 40 µg as compared to those received 20 µg HBV vaccine (87.58 ± 54.79 and 56.12 ± 19.62 respectively p -value < 0.05) and these findings agreed with Chlabicz *et al*^[21].

Regarding the non-responders in control group, 10 out of 11 individuals (about 90.9%) had positive HBsAb titer after single booster dose (20 µg) HBV vaccine.

In conclusion: Chronic HCV patients showed lower response rate for standard doses of HBV vaccine especially with advancing age, diabetes and hypoalbuminemia and a double booster dose (40 µg) vaccine would be recommended for them which is better than revaccination with the standard 3 doses recombinant HBV vaccine.

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