

ORIGINAL ARTICLE

THE RESPONSE TO HEPATITIS B VIRUS VACCINE IN HIV-INFECTED PATIENTS

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Background – HBV infection is preventable by effective vaccination in general population, but response to vaccine among the HIV-infected people seems to be low.

Methods – In this study, 48 HIV-positive patients who did not have a history of HBV infection received the conventional three-dose HBV vaccine (each dose: 20 µg) in HIV/STI/IDU Counseling and Care Center of Kermanshah Province, Iran. Anti-HBs levels were measured two months after the last dose. The sample gathering method was a random sample size. All the patients gave informed consent before entering the study. For statistical analysis, Chi-square test was performed and $p < 0.05$ was considered significant.

Results – Only 14 (29.1%) of the 48 vaccinated HIV-infected patients had positive anti-HBs titers. Among them, 11 (78.6%) were males and 3 (21.4%) females. The mean number of CD4+ T-lymphocytes per milliliter of blood was 351.5 in responders and 283.9 in nonresponders. There was a significant difference between the response to vaccine and immunologic stages of HIV infection. There was a significant statistical difference regarding sex, as 42.5% of the females responded to vaccine while this rate was 24.9% among the males.

Conclusion – The HIV-infected patients have a lower response rate to the conventional three-dose HBV vaccine compared with the general population and we recommend higher and more booster doses in early immunologic stages of HIV infection.

Archives of Iranian Medicine, Volume 6, Number 4, 2003: 269 – 272.

Keywords • HIV infection • HBV • HBV vaccine • efficacy

Introduction

Hepatitis B virus (HBV) is not an opportunistic infection in human immunodeficiency virus (HIV)-positive patients, but due to the same route of transmission, it is a common pathogen in this group.^{1, 2} Coinfection with HIV and HBV in developed countries most commonly occurs among intravenous drug users.³ Hepatitis B virus is the most common preventable viral agent in HIV-infected patients.⁴ The rate of HBV infection among HIV-positive patients is about 20% in contrast to the less than 5% prevalence rate of HBV in general population.⁵ Indeed, the risk of

chronic complications of HBV infection increases to fourfold when HIV patients are infected with this virus.^{5, 6} The rate of hepatitis D infection is also increased to about 70% in intravenous drug users, a great majority of whom are HIV infected too.^{7, 8} Prophylaxis for HBV infection in HIV-positive cases by vaccination can prevent HDV infection too. Patients with HIV and HBV coinfection are at high risk of acquiring hepatitis G, whereas this infection is not common among HIV and HCV coinfection.⁹ HBV infection in HIV-positive individuals is associated with a high rate of progression to cirrhosis and hepatocellular carcinoma.¹⁰ About 95% of patients with HIV infection have serologic evidence of previous HBV infection demonstrable by positive anti-HBs or anti-HBc serologic tests while more than 15% of them are chronic HBsAg carriers.^{11, 12}

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The Response to HBV Vaccine in HIV-Infected Patients

Table 1. The response to HBV vaccine by sex in the HIV-infected patients.

Anti-HBsAb	Positive		Negative		Total	
	No.	Percentage	No.	Percentage	No.	Percentage
Sex						
Male	11	22.9	30	62.7	41	85.6
Female	3	6.2	4	8.2	7	14.4
Total	14	29.1	34	70.9	48	100

The response to treatment rate of the patients coinfecting with HIV and HBV is poor and is about one-fifth of the response to treatment rate in HBV-infected patients without HIV infection.^{13, 21}

It is more than one decade that an effective vaccine has been developed for HBV infection resulting in protective immunologic response rates as high as 96%.^{13, 14}

The response rate to HBV vaccine in over-40-year-old individuals, those with end-stage renal disease, cirrhotic patients, and post-liver transplantation cases is lower than that in general population and they are advised to receive higher (40 µg) and additional booster doses of the vaccine.¹⁵ Due to the importance of HBV prophylaxis in high-risk groups, particularly HIV-infected patients, we evaluated the response to HBV vaccine among HIV-positive cases and its relation to different variables such as age, sex, history of drug abuse, and immune status.

Patients and Methods

In this prospective study, of all registered cases of HIV in Kermanshah Province, 48 HIV-positive patients whose diagnosis had been confirmed with enzyme-linked immunosorbent assay (ELISA) (Behring Kit, Germany) and western blot were randomly selected.

All patients were negative for HBsAg and HBsAb by ELISA and none had a history of HBV vaccination. All patients received three intramuscular (20 µg) doses of HBV vaccine at months 0, 1, and 6 (1 mL of recombinant vaccine [Herber Biotec, Cuba] was deeply injected into the deltoid muscle), and anti-HBs titer was measured two months after the last dose (a 5-mL blood sample was collected and sent to the Central Laboratory of Kermanshah Blood Transfusion Center for measurement of anti-HBs level using ELISA; anti-HBs titers more than or equal to 10 IU/L were considered positive). Flowcytometric

analysis of T-cell subsets was performed for 43 patients before vaccination. Flowcytometric analysis of peripheral blood lymphocytes was performed using fluorescence-activated cell sorter (FACS) caliber flowcytometry (Becton-Dickinson, Mountain View, California, USA). The sample gathering was a randomized sample size. For statistical analysis, Chi-square test was performed and $p < 0.05$ was considered significant.

Enrolment of the patients was independent of disease stage or degree of immunosuppression. One clinician recorded the highlights of the medical history and physical examination of each patient on a detailed questionnaire. All study variables were extracted from these questionnaires.

All the patients gave informed consent before entering the study. The patients' names and private data were remained secret.

Results

Only 14 (29.1%) of the 48 vaccinated HIV-infected patients had positive anti-HBs titers. Among them, 11 (78.6%) were males and 3 (21.4%) females. All male patients but no females were intravenous drug users. Among nonresponders, 30 (85.3%) and 4 (14.7%) were males and females, respectively. All men and 2 women in the latter group were intravenous drug users (Table 1).

There was no significant statistical difference between the patients more than 40 years old and those of other age groups among either responders or nonresponders (Table 2).

The mean number of CD4+ T-lymphocytes per milliliter of blood was 351.5 in responders and 283.9 in nonresponders.

Three of the 17 patients (17.6%) with CD4+ cell counts between 200 and 500 per milliliter and 3 of the 7 patients (42.8%) with CD4+ cell counts more than 500 responded to vaccine appropriately.

Table 2. The response to HBV vaccine by age in the HIV-infected patients.

Anti-HBsAb	Positive		Negative		Total	
	No.	Percentage	No.	Percentage	No.	Percentage
Age group						
< 20	—	—	1	100	1	100
20 – 40	10	30.3	23	69.7	33	100
> 40	4	28.5	10	71.5	14	100
Total	14	29.1	34	70.9	48	100

Table 3. The response to HBV vaccine by immunologic status (CD4+ T-cell count) in the HIV-infected patients.

CD4+ T cell	CD4 < 200		200 < CD4 < 500		CD4 > 500	
Response to vaccine	No.	Percentage	No.	Percentage	No.	Percentage
Anti-HBsAb -	14	82.4	13	68.5	4	57.2
Anti-HBsAb +	3	17.6	6	31.5	3	42.8
Total	17	100	19	100	7	100

There was a significant difference between the response to vaccine and immunologic stages of HIV infection ($p < 0.05$) (Table 3).

Discussion

As this study indicates, the response rate to HBV vaccine in HIV-infected patients is 29.1%. This rate is about one-third of that observed in general population (96%).¹⁶ This is in accord with other studies which demonstrated poor response rates to the vaccine among HIV-infected individuals.^{17,18}

The frequency of nonresponders in immunocompetent persons is 2.5 – 5% in comparison with 40% among HIV-infected cases.¹⁹ This rate is even higher (50%) among HIV-positive persons vaccinated with plasma-derived vaccines.²⁰ In the present study, the frequency of nonresponders (70.9%) is higher than that found in other reports.¹⁹ Compared with other studies, intravenous drug use was a more prevalent underlying risk factor for HIV transmission in this study that may explain the lower response rate to HBV vaccine.

There was a significant statistical difference between the rate of response to vaccine in females (42.5%) and males (24.9%) ($p < 0.05$). This may be explained by the higher rate of intravenous drug use in males (100%) in comparison with that in females (30%). It seems that intravenous use of heroin and the similar substances have independent effects on immune response; however, this hypothesis itself needs more investigations. There was no difference in the response to HBV vaccine between HIV-infected patients aging more than 40 years (71.5%) and those of other age groups (70.6%). This result is in contrast to other studies that have demonstrated low response rates to HBV vaccine among people aged more than 40 years old.¹⁵ Thus, it seems that HIV infection per se is a more important factor than age in unresponsiveness to HBV vaccine. There was a significant difference in the response to HBV vaccine among different CD4+ T-cell counts as an indicator of cellular immune status in this study. The mean CD4+ T-cell count (per millimeter of blood) in the responders was 352.5

in comparison with 283.9 among the nonresponders ($p < 0.05$). This is in accord with other studies that showed a direct correlation between CD4+ T-cell count and immune response to HBsAg.¹⁸ Otherwise, the rate of response to HBV vaccine differs among HIV-infected patients with various counts of CD4+ T cells.¹⁹

In this study, the response rate was 17.6% in AIDS or the late stage of HIV infection (CD4 < 200), 31.5% in the intermediate stage (200 < CD4 < 500), and 42.8% in the early stage (CD4 > 500). This is an important finding indicating that as the cell-mediated immunity declines, the vaccine productivity lowers too. This fact puts emphasis on the vaccination of HIV-infected patients with HBV vaccine in the early stages of infection. Thus, HIV-infected persons in the AIDS phase have a very low chance of response to vaccine.^{21,22}

In conclusion, we recommend further studies to evaluate the following topics:

1. The immune response to HBV vaccine in the HIV-infected patients with double dose of vaccine (40 µg).
2. Comparative study of HBV vaccine efficacy in intravenous drug users with and without HIV infection.
3. Evaluation of HBV vaccine responsiveness in the nonresponders with double dose vaccine, another 3-dose HBV vaccination, or giving a fourth dose of vaccine as booster.
4. Comparison of HBV vaccine efficacy in the HIV infected patients having different risk factors (risky sexual behavior, drug abuse, etc).
5. Evaluation of the role that HBV vaccine may play in immune suppression and HIV replication as well as the efficacy of HBV vaccine in the HIV patients treated with highly-active antiretroviral therapy (HAART) which has resulted in immune reconstitution (CD4 > 500).

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