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ORIGINAL ARTICLE

Immunogenicity of recombinant hepatitis B vaccine in health care worker of Boo-Ali hospital in Tehran, Iran, 2002-2004

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ABSTRACT

Background: Although recombinant hepatitis B vaccine is effective in a majority of population, a significant percent may do not response (up to 10%). Old age, obesity, heavy smoking and immunologic impairment have been associated with lower anti –HBs responses. In the present study, the efficacy of vaccine and effects of the abovementioned factors have been evaluated.

Materials and methods: Of 111 health care workers in Boo-Ali hospital, 72 participants completed primary vaccination series and antibody tittering. They received 20μg of recombinant HBV vaccine (Heberbiovac, Cuba) in standard schedule. Anti-HBs was determined by ELISA test (Diakey, South Korea) one month following the third dose.

Results: The lowest completion rate was reported among nursing staff and physicians (17%). Seroprotection (anti-HBs ≥10IU/L) was achieved in 86.1% of participants. Among seroprotected individuals, 52.8% were low-responders (anti-HBs titer of 10-99IU/L) and 33.3% were good responders (anti-HBs titer of >100IU/L). The independent predictors of responsiveness were age less than 40 (OR=3.5, 95%CI=1.8-14.6, p<0.05), non-smoking status (OR=2.9, 95%CI=1.5-17.2, p<0.05), and body mass index less than 25kg/m^2 (OR=4.3, 95%CI=1.9-18.0, p<0.05). Of 10 non-responders, 7 received booster dose while anti-HBs titer was determined only in one.

Conclusion: The primary factors associated with completion of immunization may not be amenable to job-education level. Non-compliance among non-responders was quite high (90%). This situation seems to be grim for health care workers and warranted appropriate interventions.

Keywords: *Health care worker, Hepatitis B vaccine, Seroprotection*.

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INTRODUCTION

Approximately 5% of world populations are infected with hepatitis B virus (HBV) (1). In Iran, social, medical and economic consequences of chronic hepatitis B are staggering. This disease may lead to cirrhosis, portal hypertension and hepatocellular carcinoma in a sizable proportion of infected subjects and may even cause death due to fulminant disease (1).

Universal vaccination has significantly decreased the HBV carrier and infection rate. HBV infection was hyper endemic in Taiwan and after universal vaccination, the prevalence of HbsAg among person younger than 15 years of age

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decreased from 9.8% in 1984 to 0.7% in 1999 (2). In Italy, following the program of mass vaccination, the incidence of acute hepatitis B per 10^5 population declined from 5.4 in 1990 to 2 in 2000 (3).

An important reduction in HBV-induced morbidity and mortality was achieved with the introduction of an effective vaccine. However, 2 to 10% of healthy adults do not response to vaccination with the production of protective antibody (assumed as protective: anti-HBs>10IU/L) (4). Older age, obesity, heavy smoking and immunological impairment have been associated with lower anti-HBs response (1).

Individually determined anti-HBs levels (IU/L) strongly depend on the test reagent and the vaccine under study (5). Anti-HBs titers fall with time after vaccination. The higher the anti-HBs titer after vaccination, the longer anti-HBS persists (1). In one study, the titer decreased below level of protection after 3 years in 34.5% of subjects who had initially acquired protective antibody titers (6).

Health care worker who failed to seroconvert after the third dose should be revaccinated. Revaccination was shown to result in anti-HBs response in more than 50% of person. In one study, 86.3% of non-responders developed protective anti-HBs titers after a booster dose (7).

Completion of hepatitis B vaccination may be influenced by higher income, female gender, white race and not having smoked cigarettes. Site of care, risk factors for acquiring HBV, and disease and vaccine knowledge are not associated with completion rate (8).

PATIENTS and METHODS

The present study was conducted in Boo-Ali hospital in Tehran between 2002 and 2004. Totally, 111 health care workers were selected by cluster random sampling, among whom 72 participants completed primary vaccination series and antibody tittering were negative for HBs-Ag and other serological markers of hepatitis B.

They were requested to complete an informed consent, then, 20μg of recombinant hepatitis B vaccine (Heberbiovac, Cuba) was administered intramuscularly at a dosing schedule of 0, 1 and 6 months. Serum anti-HBs antibody titers was determined at 30 days after the third dose of vaccine using a quantitative ELISA kit (Diakey, South Korea).

Protection with hepatitis B vaccination was considered to be achieved when anti-HBs antibody concentration of more than 10Iu/L was detected. Non-responder was defined as mean anti-HBs antibody titers of less 10IU/L. Titers between 10-99IU/L were considered as low-responders while anti-HBs titer of ≥100IU/L were good responders.

The statistical analysis was preformed using exact Fisher test by SPSS (Version 10.0, SPSS company, USA). The level of significance adopted for all tests was 5% ($p<0.05$).

Multiplying all the values and taking $1/n^{th}$ of net value estimated the geometric mean titers. Taking log values did calculation and then antilog of these values estimated geometric mean titers (GMT). Body mass index (BMI) was calculated by: weight (kg)/(height)^2 (m)). Obesity was defined as BMI more than 30kg/m^2 and over weight subjects were those with BMI between 25-30kg/m^2.

RESULTS

Totally, 72 subjects (64.8%) of 111 eligible participants had completed the vaccination series and tittering. The lowest completion rate was found in nursing staff and physicians (figure 1).

Of 72 health care workers who have completed primary series of vaccination, 10(13.9%) were non-responders. Among seroprotected individuals, 38 (52.8%) were classified as low responder and 24 (33.3%) as good responder.

Furthermore, immune response was determined in three age groups; "A" (20-39 years), "B" (40-50 years) and group "C" (>50 years). In groups "B" and "C", immune response was reported 78.3% and 77.8%, respectively; however, 92.5% of patients in group "A" showed immune response. Indeed, subjects aged less than 40 years revealed significantly better immune responses (OR=3.5, 95%CI=1.8-14.6, p<0.05).

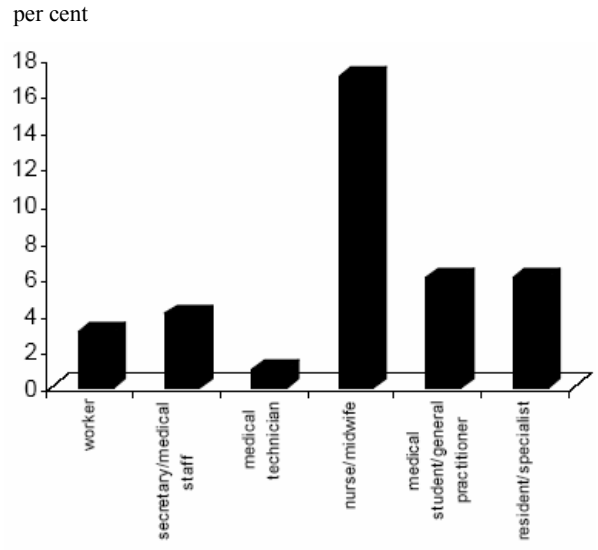

Figure 1. *Frequency of non-compliance based on job-education level in health care workers in Boo-Ali hospital, 2002-4.*

Females have shown slightly better immune response when compared with males (87.5% vs. 81.3%), however, their difference did not reach a statistically significant level. Seroprotection among smokers was 71.4% as compared with 85.9% of nonsmokers (OR=2.9, 95%CI = 1.5-17.2, p<0.05).

Our results revealed that immune response is influenced by obesity. Seroconversion in obese (BMI>30kg/m^2) and over weight subjects (25kg/m^2<BMI<30kg/m^2) was 71.4% and 77.3%, respectively; however, immune response was reported in 93.2% of non-obese (BMI≤25kg/m^2) individuals (OR=4.3, 95%CI=1.9-18.0, p<0.05).

Among 10 non-responders, 7 cases were received at least one booster dose (70%) and, fortunately, one of these booster dose recipients showed anti-HBs titer greater than 100IU/L. Finally, geometric mean titer was calculated 48.8%.

DISCUSSION

The lowest completion rate was reported in nursing staff and physicians. It could be partly explained by greater sample size of this group (49%). Health care workers are at increased risk of HBV infection, thus, HBV vaccine compliance is of utmost importance for this group. Since HBV infection may be acquired through percutaneous or mucosal exposure to blood or body fluids of infected persons, a comprehensive strategy to eliminate HBV transmission by increasing vaccination compliance seems to be necessary for all health care workers especially nursing staff. Non-compliance was reported in 30.8% of physicians. These finings are not in accordance with earlier study of Middleman *et al.* who had explained the association between completion rate and income, female gender, and white race (8). The present study demonstrated a similar non-responsiveness (13.9%) that is comparable with prior studies (2-10%) (1,4,7). Older age was shown to be correlated with lower anti-HBs responses. Subjects aged less than 40 years have shown better immune response (OR=3.5). Thus, we recommend four dose regimen vaccine at months 0, 1, 2, 6 or 12 for individuals aged ≥40 years.

On the other hand, Halota concluded that women respond better than men (9), however, other studies failed to show sex as an influencing factor for immune response to hepatitis B vaccine. Similarly, we did not find any significant statistical difference between male and female gender.

Immune response in smokers was about 2.85 times less than non-smokers. For smokers, smoking

cessation is a far more powerful means of reducing risk of cardiovascular disease as well as improving immune response to hepatitis B vaccine.

Furthermore, immunogenicity in obese and over-weighted subjects was 4.2 times less than non-obese candidates. Undoubtedly, exercise could not only reduce body weight and cardiovascular risk significantly, but also may improve immune response to vaccine.

Health care workers should be informed that they have failed to seroconvert after vaccination; thus, they should receive HBIG for significant future exposure to HBV since they remain susceptible to HBV infection.

Of 10 non-responders, 7 received booster dose while anti-HBs titer was determined in one (14.3%). This is a grim situation for health care workers due to low safety blood handling practice in our country. Kunaldas and colleagues concluded that a single booster dose after 6 months in primary non-responders lead to good seroprotective antibody titer (10). Other studies, however, showed revaccination of individuals who have non-detectable anti-HBs response after the third vaccine dose of a primary immunization series and reported anti-HBs response in more than 50% of subjects (1). We recommend a single booster dose in non-responders and determination of antibody response one month later. However, among non-responders revaccination services should be completed and immune response should be determined one month following the last dose. Non-responders of second vaccination series should be recommended for HBIG after a high-risk exposure.

Finally, geometric mean titer was about 48.8% that is low when compared with titers reported in other studies (10-12). This low titer may be related to the test reagent or vaccine itself; however, the implication of this titer is still under study.

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