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Original Article

LOW-DOSE HEPATITIS B VACCINATION WITH RECOMBINANT VACCINE IN IRANIAN HEALTH CARE WORKERS

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Background – **Hepatitis B and its sequelae are among the most important public health hazards in Iran and other developing countries. Although effective vaccines are available, the high cost of the vaccines has remained an obstacle to their use. The present study was designed in order to evaluate modification of vaccination schemes as a cost-reduction strategy.**

Methods – **The study was a randomized clinical trial in which 182 healthy adults occupied in health care services with no previous exposure to hepatitis B virus volunteered to be enrolled. The subjects were vaccinated with a recombinant HB vaccine using four different vaccination schemes. The rates of seroconversion as well as the levels of anti-HBs titers in the four schemes were compared.**

Results – **Although the seroconversion rate and nonresponsiveness were the same in all of the 4 groups (97.6%, 97.8%, 96%, and 97.2%; $p > 0.5$), the concentration of anti-HBs was significantly lower in the groups vaccinated intradermally compared to the groups vaccinated intramuscularly (means: 675 vs 3,200 IU/L, $p < 0.01$).**

Conclusion – **Replacing the second and third injections in the regular scheme of recombinant HB vaccine with two intradermal injections of 2 µg (one-tenth of the regular dose) results in the same seroconversion rates and the same level of anti-HBs as the regular scheme .**

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Introduction

Hepatitis B virus (HBV) infection and its sequelae including chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) are supposed to be among the most important public health hazards in Iran. It is estimated that around 2.6% of Iranian population are HBV carriers and 67.8% of chronic hepatitis and 82% of HCC cases are positive for at least one of the serological markers for HBV.[1, 2]

The neonatal vaccination program was launched in Iran in 1992. The program is expected to reduce the HBsAg carrier rate in children similar to what was reported in Saudi Arabia where a drop from 6.7% in 1989, when neonatal vaccination started, to 0.3% in 1997 was demonstrated.[3] However, despite the availability of an effective vaccine, the vaccine cost remains one of the major obstacles to further implementation of HBV vaccination programs. As a consequence of underutilization of HBV vaccine, HBV infection continues to be an important occupational health risk as well as a public health problem in Iran and worldwide.[2]

Immunization by intradermal (ID) route is a recognized strategy for inducing immunity with small amounts of antigen (through Langerhans cells in the skin which capture the antigen and replace macrophages in inducing T-lymphocyte response) and has been successfully used in several studies.[4 – 7] However, the success of this scheme is dependent on the type of vaccines, the populations studied, and the protocols employed.[4]

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The present pilot study was designed in order to obtain a better insight into the feasibility of a cost-reduction strategy for vaccination of health care workers as an important high-risk group requiring HB vaccination in Iran.

Patients and Methods

The subjects were 210 health care workers employed in the hospitals and medical centers in Arak, the central city of Markazi Province in Iran, who voluntarily enrolled in this randomized trial from 1996 to 1997.

A general physical examination was carried out on all of the participants and all individuals recognized as healthy by the medical definitions were included in the study. These participants were then tested for HBV serological markers (HBsAg, anti-HBs, and anti-HBc) and all individuals recognized as healthy by medical definitions were included in the study.

Finally, the study began with 182 subjects (mean age: 26.5 years, age range: 21 to 35 years). A blood sample was taken before vaccination. The participants were then randomly divided into four groups, each receiving one of the four vaccination schemes that follow below:

- Group A: three intradermal 2-µg doses at months 0, 1, and 6;
- Group B: three intradermal 4-µg doses at months 0, 1, and 6;
- Group C: one intramuscular 20-µg dose at month 0 followed by 2 intradermal 2-µg doses at months 1, and 6; and
- Group D: three intramuscular 20-µg doses at months 0, 1, and 6 (the regular schedule proposed by the manufacturer).

The vaccine used was recombinant Engerix B from Smith Kline Biologicals, Belgium.

All of the 182 cases who entered the vaccination programs completed the study.

Serologic tests

All HBV markers were tested before vaccination using ELISA kits (Organon Teknika, Amsterdam, the Netherlands).

A 5-mL blood sample was taken before the second and third doses of the vaccine and another one three months after the last dose. Seroconversion was tested by quantifying serum anti-HBs levels using ELISA kit and the results were reported in IU/L. The levels of anti-HBs above 10 IU/L were defined as protective.

Statistics

Chi-square and Fisher exact tests were used to compare the serological responses and mean titers obtained in the groups. A p value of less than 0.05 was considered as statistically significant.

Results

The results obtained from the 4 vaccination groups are summarized in Table 1. As demonstrated, the frequency of responders (anti-HBs > 10 IU/L) was similar in all four groups (p > 0.5) and no significant difference was observed in antibody response between males and females. The mean titers of anti-HBs (IU/L) observed in male vs female was group A 715 vs 635, group B 700 vs 910, group C 2,050 vs 2,900, and group D 3,500 vs 2,900 (p > 0.2 in all cases).

It is noted that the increase in the amount of antigen injected intradermally did not make any significant difference in the response rate or the final mean titer of anti-HBs observed after

Table 1. Comparison of antibody response in the four vaccination schemes.

Group	Vaccinees (No.)	Sex M/F	Responders *n* (%) after 1st, 2nd, and 3rd injections	Mean titer IU/L (SD) after 1st, 2nd, and 3rd injections
A			1) 7 (16.5)	1) 82.6 (29.3)
(2 µg ID)	42	14/28	2) 36 (85.7)	2) 91.4 (173.8)
at 0,1, and 6 months			**3) 41 (97.6)**	**3) 675.65 (620.2)**
B			1) 8 (17.3)	1) 70.5 (130.4)
(4 µg ID)	46	16/30	2) 39 (84.7)	2) 137.8 (121.74)
at 0,1,6 months			**3) 45 (97.8)**	**3) 712.5 (517.6)**
C			1) 8 (16.3)	1) 59.2 (130.1)
(20 µg IM + 2 × 2 µg ID)	49	22/27	2) 41 (83.6)	2) 103.4 (196.4)
at 0 1, and 6 months			**3) 47 (96.0)**	**3) 2498.7 (3924.3)**
D			1) 3 (6.6)	1) 50 (30.5)
(20µg IM)	45	20/25	2) 33 (73.3)	2) 123.27 (302.9)
at 0, 1, and 6 months			**3) 44 (97.7)**	**3) 3191.8 (4024.5)**

ID= intradermal; IM= intramuscular.

completion of vaccination (675 vs 712 IU/L, $p > 0.05$). However, in group C where one intramuscular 20-µg dose was followed by 2 intradermal 2-µg doses, the immune response was improved, demonstrated by a significant rise in anti-HBs concentration (675 vs 2,500 IU/L, $p < 0.001$). The mean anti-HBs titer in group C was similar to that in group D (receiving the regular vaccination scheme of three intramuscular 20-µg doses at months 0, 1, and 6) (2,500 IU/L vs 3,200 IU/L, $p = 0.2$). In fact, the immune response (measured by the two parameters: the frequency of seroconversion and mean anti-HBs concentration) in group C was similar to that in group D which received the regular full-dose scheme.

Discussion

The purpose of this study was to compare the immunologic response of healthy individuals vaccinated with low-dose intradermal injections with that of the individuals who received 3 full-dose intramuscular injections. The data in literature concerning this subject has been controversial. Redfield et al[5] have demonstrated that intradermal doses of HB vaccine resulted in a seroconversion rate similar to that following the regular intramuscular schemes. However, other investigators found that the rate of seroconversion in intradermally vaccinated recipients was similar to that of those vaccinated intramuscularly though the former developed lower anti-HBs concentrations.[4, 6, 7] In contrast, other studies report no significant difference between anti-HBs concentrations following intradermal or intramuscular vaccination.[8, 9] Race, genetic factors, and type of vaccines used may account for the difference in the results obtained from various studies. Thus, the present study was designed and carried out with an available vaccine in a high-risk Iranian population who required to be vaccinated.

Different vaccination protocols were evaluated in this population and the results confirmed that 2-µg intradermal doses (10% of the standard dose) are as effective in producing protective levels of anti-HBs (>10 IU/L) as the regular intramuscular doses and that increasing the dose of the vaccine to 4 µg had no effect on the overall seroconversion rates. These findings are in accordance with a study which reported a 97% antibody response rate in children immunized by intradermal protocols,[10] and a Canadian study reporting a 99% seroconversion rate nine months after intradermal vaccination in a group of health care workers.[11] However, a similar study in Sweden reported only a 68% seroconversion rate after 3 doses of intradermal vaccination and 89% after 4 doses.[12] Another similar study on Iranian neonates also reported a 96.2% seroconversion rate after intradermal vaccination compared to 98.1% in intramuscular vaccines.[13] In addition, a 95.8% seroconversion rate for intradermal vs a 98.8 rate for intramuscular vaccination has been reported in Iranian female high school students.[14] In the present study, it is noteworthy that the concentration of anti-HBs was lower in the recipients of intradermal vaccination after 3 doses despite equal seroconversion rates in intradermal and intramuscular schedules. This is consistent with the findings of some other investigators.[4, 6, 7]

It has been proposed that low antibody levels may be a factor affecting the duration of the antibody response after low-dose intradermal immunization.[4] Although data in this regard are limited, one study has reported that anti-HBs concentrations above 10 IU/L persisted in 63% of medical students immunized intradermally with low doses of the plasma-derived vaccine 30 months after the initial dose.[15] This finding is consistent with another study where 85% of the medical students intradermally vaccinated with 2-µg doses had more than 10 IU/L of anti-HBs concentrations 24 months after immunization.[4] The importance of the level of anti-HBs on its duration has also been underlined by another group of investigators who found that most vaccinees with the peak concentrations below 100 IU/L had the titers less than 10 IU/L after two years whereas 96% of those with the peak concentrations above 1,000 IU/L had the levels higher than 10 IU/L after 48 months.[16, 17] Considering these findings, it can be concluded that low-dose intradermal protocols can be used to achieve immune protection. However, it seems that the schedule used for group C in our study where a first full-dose (20 µg) intramuscular injection was followed by two 2-µg intradermal doses is a better choice in order to achieve sufficient titers with a higher probability of longer duration of immunity. The reason is that in this group, the mean titer of anti-HBs is higher than 1,000 (2,500) IU/L and similar to that in the regular intramuscular schedule; this may reduce the necessity of booster doses. In fact, the higher cost for this group that received one full-dose intramuscular injection (as compared with the schedules A and B where only low-dose

intradermal injections were used) may be compensated by the cost saved from the lower need for booster doses. In an experience in Gambian children, it was also shown that the protective levels of antibody developed in 84% of children immunized with three intradermal doses. However, the immune response rate was improved to 94% when the first injection was changed to a full intramuscular dose.[18]

Finally, considering the similar protective outcomes of intradermal and intramuscular routes of HB vaccine administration and the lower cost of intradermal route, the use of the latter should be seriously considered.

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