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ORIGINAL ARTICLE

Comparison of Two Recombinant Hepatitis B Vaccines

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Background and Aims: Hepatitis B virus (HBV) infection is an important public health problem. Hepatitis B vaccine induces protective response in the majority of vaccinated persons. In our country, we do not have any evaluation for the efficacy of each type of vaccines used in adult and our objective was therefore to evaluate the efficacy of vaccines.
Methods: In a randomized double-blind clinical trial 347 military personnel and their family in Kashan city, central Iran, were studied during August 2007 to April 2008. Participates who did not have history of HBV vaccination were included in this study. Five-mL blood samples were taken from each person and tested for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb) and total hepatitis B core antibody (HBcAb). If the test results were negative, they were then divided into two groups and vaccinated with either recombinant Cuban or Korean vaccine. One month after the latest vaccine dose, we assessed the antibody to hepatitis B surface antigen (anti-HBs Ab) titer.
Results: 347 subjects (207 men, 140 women) were studied. All participants were more than 15 years old. The mean±SD age of participants was 32.3±7.2 years. The mean±SD titer of anti-HBs Ab was 253.6±95.4 MIU/mL in Cuban group and 315.7±163.5 in Korean vaccine group ($P<0.001$). The Korean vaccine induced a higher titer of antibody in ages less than 40. Four (2.3%) subjects in the Cuban and 2 (1.1%) in the Korean vaccine group did not develop protection.
Conclusions: The Korean vaccine induces more protection and higher titer in subjects aged less than 40 years than the Cuban vaccine. Therefore, we believe that the Korean hepatitis B vaccine is a better choice in comparison to the Cuban vaccine for prevention of hepatitis B virus infection and mass vaccination in our country.
Keywords: Hepatitis B Vaccine, Hepatitis B Virus, Heberbiovac-HB

Introduction

Hepatitis B virus (HBV) infection is an important public health problem in the world. Recent estimates has shown that more than two billion people are infected with HBV globally and that the infection is supposed to be causally related to one to two million deaths per year worldwide. More than 350 million people are chronic carriers of HBV [(1)]. Prior to the implementation of vaccination programs, the lifetime risk of HBV infection exceeded 60% in areas with high prevalence of the disease, such as China, Southeast Asia, and Africa [(2)]. Hepatitis B vaccination has been one of the success stories of the 20th century and has been extensively used in a wide range of groups throughout the world and it has successfully reduced the prevalence of hepatitis B infection [(3)]. Three different classes of hepatitis B vaccine are available based upon how they are derived (*i.e.* from plasma, yeast, or mammalian cells). The first generation HBV vaccine was prepared by concentrating and purifying plasma from hepatitis B surface antigen (HBsAg) carriers. This vaccine has excellent efficacy and safety.

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However, it suspected to transmit blood-borne infections. As a result, it is no longer used in most developed countries [4, 5].

The second generation HBV vaccine is yeast-derived recombinant vaccines. They are produced by cloning of the HBV S gene in yeast cells. The recombinant vaccines contained thimerosal as a preservative. Then, two yeast-derived recombinant thimerosal-free vaccines have been developed (Recombivax HB and Engerix-B) which are widely available [6, 7].

The third class of HBV vaccine is the mammalian cell-derived recombinant vaccine. Three vaccines of this class have been developed. In addition to the S antigen, one of these contains antigen from the pre-S_2 region while the other two contain antigens from both the pre-S_1 and pre-S_2 regions. Although vaccines with pre-S antigen may have more immunogenicity they are not widely available. Currently, vaccination is one of the most important preventive measures for HBV infection [8, 9].

In Iran, the prevalence of chronic carrier state of hepatitis B infection has been reported to be 2.5%-3%. The rate has been reduced since establishment of the National HBV vaccination program in 1993 for all neonates [10] and high risk groups of adults such as military personnel [11]. In our country, we first used plasma derived vaccine and then recombinant vaccine [12, 13]. Hepatitis B vaccines induce protective response in the majority of vaccinated persons, however, 1%-10% of both adults and neonates fail to response depending on the use of differ recombinant vaccines, as one factor. We do not have any comparative study on efficacy of each type of HBV vaccines imported from other countries such as Cuba (Heberbiovac HB vaccine) and Korea (Hepavax-Gene vaccine). The objective of this study was to investigate the effect of Cuban (Heberbiovac HB) and Korean (Hepavax-Gene) vaccines in adult and middle-aged persons after three doses of each vaccine.

Materials and Methods

A randomized double-blind clinical trial was conducted on military personnel and their family in Kashan, Isfahan province, Central Iran during August 2007-April 2008. Those people who did not have any history of HBV vaccination, HBV infection, use of immunosuppressive agent, HIV infection, steroid therapy, addiction and acute viral infection at the time of vaccination, were included in this study. Participants gave informed written consents prior to the administration of the vaccine. This project was approved by the Ethics Committee of Research Departments of Baqiyatallah University of Medical Sciences (project No: 87-481-June-2008 of Health Research Center). In the calculation of the sample size of 328 (164 samples for each vaccine), we assumed an expected seroprotection rate of more than 96% in hepatitis B vaccinated persons in Iran [13]. Demographic data collected from each person included age and level of education. Five-mL blood samples were taken from each participant and assessed for HBsAg, hepatitis B surface antibody (HBsAb) and total hepatitis B core antibody (HBcAb); if the test results were negative, then the participants were vaccinated. HBsAb, HBsAg and HBcAb were assessed with enzyme-linked immunosorbent assay (ELISA; Equipar, Italy). The participants were divided into two randomized groups and vaccinated with adult dose of 20 g of HBsAg with either recombinant Cuban (Heberbiovac HB, Heberbiotec, Havana, Cuba) or Korean (Hepavax-Gene, Green Cross vaccine Corp, Korea) vaccine. One mL of each of these vaccines contains 20 g of purified HBsAg, 0.5 mg aluminum hydroxide and 0.05 mg thiomersal.

The vaccines were administered intramuscularly in the deltoid muscle on 0, 1, and 6 months. One month after the last dose, we assessed the antibody to hepatitis B surface antigen (anti-HBs Ab) titer. Titers equal or more than 10 MIU/mL were considered as appropriate immune response and "protection"; titers below 10 MIU/mL were considred as seroconversion but "no protection". Side effects after vaccination such as fever, local pain, allergic reaction, erythema and local cellulites were recorded.

Statistical analyses were done with the SPSS® v.13 for Windows®. Rates of seroconversion or seroprotection were compared between each group by two-tailed Fisher's exact test and ^{2}. Mann-Whitney U test was used for comparison of means between the two groups. $P<0.05$ was considered statistically significant.

Results

During the study period, we studied 347 (207 male, and 140 female) military personnel and their families. The mean±SD age of participants was 32.3±7.2 (range: 15-51) years; 295 (85%) of persons were less than 40 years old. Most of participants (n=217, 62.5%) had diploma or less; the remaining had at least a bachelor degree. Heberbiovac HB Cuban vaccine was given to 172 (49.6%) and Hepavax-Gene Korean vaccine was administered to 175 (50.4%) persons. The

geometric mean±SD of the anti-HBs Ab titer was 253.6±95.4 (95% CI: 0.9-310.8) MIU/mL in Heberbiovac HB Cuban vaccine group and 315.7±163.5 (95% CI: 4.1-666.4) MIU/mL in Hepavax-Gene Korean vaccine group (P<0.001). Anti-HBs Ab titer in the Korean vaccine had a significant correlation with age and was higher in those less than 40 years of age. Four (2.3%) persons from the Cuban vaccine group and two (1.1%) from the Korean vaccine group failed to produce the minimum acceptable antibody level (Table 1). While men more responsive to the Cuban vaccine, women had a higher response to the Korean vaccine (Table 1). No side effects but mild local pain was observed.

Table 1. ! % ! $! ! ! " #

Men	263.2±90.8	307.7±145.3	0.015
Women	228.1±103.1	322.8±178.6	<0.001
Age<40 years	257.9±90.6	323.5±164.7	<0.001
Age 0years	238.5±110.5	226.4±120.9	0.74
Non-responders	4 (2.3%)	2 (1.1%)	0.439

Discussion

Our finding that the Korean Hepavax-Gene vaccine and the Cuban Heberbiovac HB vaccine, respectively, produced protection in almost 99% and more than 97% of people, is similar to results of other studies [14].

These two vaccines were highly efficient in antibody production, though less than 2% of participants were unresponsive. Another study reported about 5%-10% of unresponsiveness. This difference in the immunogenicity amongst the recombinant vaccines is primarily due to the differences in strain source, production, and protein purification protocols employed by the manufacturers [15]. Those who failed to produce the protective antibody level may be protected with an additional dose of the vaccine [16].

The immune response is influenced by the dosage and time of evaluation after completing the vaccination. Therefore, although the response in short-term might be similar, it is necessary to evaluate the long-term response [15].

This study showed that the Korean Hepavax-Gene vaccine induced a significantly higher antibody titer than the Cuban Heberbiovac HB vaccine. This finding was different from the results of Baldy that indicated that the Korean Hepavax-Gene vaccine with induction of high antibody titer may produce long-term protection [14].

We showed that gender had some effects on the response to vaccine; women and men who were vaccinated with the Korean vaccine developed a significantly (P<0.05) higher antibody titers than those who received the Cuban vaccine. This is in contrary to the findings of most of other studies. This difference may be due to the type of vaccine administered and younger age of persons in their studies [17, 18]. Similar results were reported by Janbakhsh *et al.* [19] which showed a response rate of 74.7% in male and 61.8% of female healthcare workers and also in a study conducted in Yazd province, Iran, which may be due to the less effectiveness of Heberbiovac HB than other similar vaccines [20].

We showed that vaccination with each type of the vaccines in ages less than 40 years induced a significantly higher titer and protection. The Korean Hepavax-Gene vaccine was also more effective than Heberbiovac HB Cuban vaccine in ages less than 40. Similar to other reports its difference was not significant in ages more than 40, which warrants addition of an added dose or a booster dose for better response in older ages [21-24] . Amongst all risk factors, higher age was the most important factor, as shown by declining in seroprotection rates [15] which may be due to cellular defects. Therefore, people should be immunized before age of 40 [19, 25-27].

The Hepavax-Gene Korean vaccine induces more protection than Heberbiovac HB Cuban vaccine and therefore vaccination with Korean may be more effective than the Cuban vaccine [28].

Hepatitis B vaccination, as part of extended program of immunization (EPI), is free of charge for children in Iran but the vaccines should be imported from other counties by the Ministry of Health. The cost of HBV vaccine is important in developing countries such as Iran; here, the price of one dose of Hepavax-Gene Korean vaccine is cheaper than one dose of Heberbiovac HB Cuban vaccine and that is why we think the Korean vaccine is better for mass vaccination [28, 29].

No local or systematic adverse reactions after vaccination were observed and the two vaccines studied are safe, as shown in another study [24]. Some reported adverse reactions in other studies with Hepavax-Gene vaccine may be due to thiomerosal preservative of this vaccine [30, 31].

One of the limitations of this study was the small sample size we studied. Therefore, conduction of a study with a larger sample sizes is warranted, although finding a large sample size of high risk

group adults who have not been vaccinated is very difficult in Iran.

Conclusions

This study showed that there is significant difference between these two types of vaccines, and Hepavax-Gene Korean vaccine had more protective effect, higher geometric titer in men, women and individuals under forty of age than Heberbiovac HB Cuban vaccine. Korean vaccine also is cheaper than Cuban vaccine and therefore we think that Hepavax-Gene Korean vaccine is the best choice for prevention of HBV infection and mass vaccination in Iran.

Acknowledgements

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References

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