Immunogenicity and reactogenicity of a recombinant hepatitis B vaccine in subjects over age of forty years and response of a booster dose among nonresponders

Kunal Das, R. K. Gupta, V. Kumar, P. Kar

Abstract

AIM: The study was initiated to evaluate the reactogenicity and immunogenicity of a recombinant hepatitis B vaccine in the age group >40 years and to study the response of a single booster dose in primary non-responders to the hepatitis B vaccination.

METHODS: A total of 102 volunteers without markers of hepatitis B infection (negative for HBsAg, anti-HBc antibody, HBeAg and anti-HBs antibodies) received 20 µg of recombinant HB vaccine intramuscularly at 0, 1, and 6 months. Anti-HBs titers were evaluated by a quantitative Elisa kit at 90 and 210 days. A booster dose of 20 µg HB vaccine was given after 6 months of the 3rd vaccine dose to the 15 non-responders and anti-HBs titers were measured after 1 month.

RESULTS: Seroprotection (anti-HBs GMT ≥ 10 IU/L) was achieved in 85.3% (87/102) volunteers. The mean GMT titers of the vaccine responders was 136.1 IU/L. Of the seroprotected individuals, there were 32.4% (33/102) responders (anti-HBs titers <10-99 µIU/ml) and 52.9% (54/102) were responders (anti-HBs titers ≥100 µIU/L). All the non-responders (15/15) responded to a single dose of the booster dose of recombinant HB vaccine and their mean anti-HBs antibody titers were more than 100.5 µIU/ml after the booster dose.

CONCLUSION: Recombinant hepatitis B vaccine offers good seroprotection in the age group >40 years and has a good safety profile. A single booster dose after 6 months in primary non-responders leads to good seroprotective antibody titers. However, larger population based studies are needed to evaluate the role of a booster dose in selected group of non-responders and whether such an approach will be cost effective.

MATERIALS AND METHODS

Volunteer selection

The study was conducted in L. N. Hospital, New Delhi over the period of one year (1996-1997). A total of 147 healthy volunteers (volunteers were attendants of the patients attending the medical OPD services) in the age group more than 40 yrs out of 387 healthy persons who were none obese and non-smokers attending the medical outpatient services consented to be included in the study. All of these volunteers were tested for markers of HBV infection. All the subjects were screened by the serological tests including HBsAg (Ranbaxy Diagnostics, India) and anti-HBc (Melotec, Spain) using commercially available ELISA kits. 102 volunteers who were negative for all the serological markers of hepatitis B infection, completed the hepatitis B vaccination programme.

HBV vaccination and sample collection

In a total of 102 volunteers after their informed consent, 20 µg of recombinant DNA hepatitis B vaccine (EnivaCHB, Panacea Biotec) was administered intramuscularly at a dosing schedule of 0, 1 and 6 months. Five dropped out after the first vaccine dose themselves, hence 102 volunteers received all the three doses of HBV vaccination. Serum samples for anti-HBs antibody titres were determined at 90 and 210 days. Anti-HBs antibodies were done using a commercially available quantitative ELISA kit (AUSAB-EIA, Abbot Labs, USA).

INTRODUCTION

Hepatitis B infection is a major public health problem worldwide due to its long-term sequelae which include chronic hepatitis, cirrhosis and hepatocellular carcinoma. The situation is grim in developing countries like India, where blood bank infrastructure is non-existent outside the major metropolitan cities and safe blood handling practice standards are low. India comes under intermediate zone of HBV prevalence, and with a carrier rate of 4.7%[1,2] has estimated 42 million carriers, next only to China. 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. Hepatitis B vaccination programmes have successfully reduced the prevalence of hepatitis B, e.g. in Taiwan, where universal HB vaccination[3] has lead to a significant reduction of hepatitis B prevalence and incidence of hepatocellular carcinoma in children. The immunogenicity, efficiency and safety profile of hepatitis B vaccine has been well established. More than 90% seroconversion has been achieved in adult populations consistently[4,5]. The safety profile of the recombinant vaccine has been very good[6]. No response to hepatitis B vaccination is increased among certain risk groups like smokers, diabetes, chronic renal failure patients, elderly obese individuals. It is important to predict vaccine non-responders as they are susceptible to break through hepatitis B infection[7]. The study was designed to evaluate the immunogenicity and reactogenicity and safety profile of a recombinant hepatitis B vaccine in subjects above the age of 40 yr and to study the response of a single booster dose in primary non-responders to hepatitis B vaccination.

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Protection with hepatitis B vaccination is considered to be achieved when concentration of anti-HBs antibody titers is more than 10 IU/L. A non-response was defined as mean anti-HBs antibody titers below 10 IU/L, low responders were those with titers between 10-99 IU/L, and those with anti-HBs titers more than 100 IU/L[13-26] were responders. A high response was on with titers more than 1 000 IU/L.

**Booster schedule**

All the non-responders (15/15) received an additional booster dose (20 µg) at 6 months after the third vaccination dose (12 months from the first vaccine dose) and the anti-HBs titers were measured after one month of booster dose.

**Statistical analysis**

Statistical analysis was done using Chi-square test and Student’s t test.

**RESULTS**

A total of 102 subjects were enrolled in the study. The mean age of the study group was 44.6±5.6 yr. with male: female ratio of 1.9:1. At day 90, after administration of two doses of recombinant vaccine 87.3 % (89/102) subjects achieved seroprotective levels of anti-HBs. At day 210 after administration of the third dose of recombinant vaccine 87/102 (85.3 %) subjects achieved seroprotective levels of anti-HBs. The mean anti-HBs titers achieved after the third dose of vaccine in the responders was 136.1 IU/L. The age distribution of mean anti-HBs levels achieved after the third dose of vaccine are given in Table 1. The peak anti-HBs levels achieved are lower in patients with increasing age. Further more, 13.3 % (11/83) subjects in the age group 40-49 years did not achieve seroprotective levels. Whereas 1/4(25 %) subjects in the age group >60 years did not respond but the difference was not statistically significant. Also the number of high responders (anti-HBs levels >1 000 IU/L) was not significantly higher in the age group 40-49 years as compared to the age group 50-59 years [85.7 % (18/21) in the age group 40-49 years and 14.3 % (3/21) in the age group 50-59 years]. The mean age of 15 non-responders was 46.4±6.9 yr which was, however, not statistically different from the mean age of responders. 11.9 % (8.67) males were non-responders whereas 20 % (7/35) females were non-responders but the difference was not statistically significant.

All the non-responders, who were given an additional booster dose of 20 µg recombinant vaccine, responded and this achieved seroprotective levels.

**Table 1** Age distribution of (GMT) anti-HBs titers

| Age (years) | Male | Mean GMT | Female | Mean GMT |
|-------------|------|----------|--------|----------|
| 40 - 49     | 52 (76.5%) | 136.0 | 30 (91.1%) | 145.4 |
| 50 - 59     | 13 (19.1%) | 105.9 | 2 (5.8%) | 177.6 |
| > 60        | 3 (4.4%) | 107.5 | 1 (2.9%) | 41.56 |
| Total       | 68 |          | 33 |          |

**DISCUSSION**

Risk factors that have been associated with non-response to hepatitis B vaccine include increasing age, male gender, obesity, history of smoking, administration of vaccine in buttock rather than deltoid [4,10-13], diabetes and chronic renal failure [14,15]. In many of the non-responders not explained by the above risk factors, certain HLA types have been found to be associated with non response [16-19]. The relationship of hepatitis B vaccination response with age is controversial. Our study suggests that seroconversion in age group >40 years is 85.7 %, which is considered high compared to most other studies [20,21] where a seroconversion rate of around 60 % has been reported. However, as all the above studies, we too found a decreasing seroconversion rate with increasing age (Table 1). Our study suggests that 85.7 % of the high responders (mean titers >1 000 IU/L) occurred in the relatively younger age groups. These findings favor the hypothesis that increasing age decreases seroprotective antibody formation after vaccination. This finding is of clinical importance as non-responders who do not develop protective antibody level remain susceptible to break-through hepatitis B infection. Although no comparative Indian study of HBV vaccine in elderly is available, reports in adults show a 90-100 % seroconversion rate for 20 µg recombinant HBV vaccine administered intramuscularly [22] not different from Western rates. For management of non-responders, there are no exact guidelines. Most unresponsive subjects are not absolute non-responders, since it has been shown that most of them can develop protective anti-HBsAg titers after a fourth or fifth dose of vaccination [23,24]. Most studies in literature have found a variable response rate of 40-60 % [25-30] to booster dose vaccination among non-responders. Our study suggests a 100 % seroconversion rate after a single booster dose that is higher than most reports in the literature. One of the reasons for higher rate of seroconversion in our study compared to other reports in literature could be: (i) volunteers had received the booster dose after 6 months from the last vaccine dose and (ii) the selection of non-obese and non-smoking volunteers. If further such reports of 100 % seroconversion are available from other centers as well, an additional vaccine dose among the older populations could be recommended routinely after evaluation of cost effectiveness of such a strategy. There were no major side effects and relatively few minor side effects viz pain at injection site, fever etc. in 36/102 (35.3 %) of the cases. To conclude, the study suggests that the recombinant HBV vaccine is highly immunogenic with good safel profile among the age group >40 yr and a single booster dose is effective in non-responders. Further larger population based studies need to be undertaken to confirm our findings.

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