P.O.Box 2345, Beijing 100023,China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

World J Gastroenterol 2003;9(5):1132-1134
World Journal of Gastroenterology
 ISSN 1007-9327

• BRIEF REPORTS •

# 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

**Kunal Das, R. K. Gupta, V. Kumar, P. Kar,** Department of Medicine, Maulana Azad Medical College & L. N. Hospital, New Delhi. Medical Advisor, Panacea Biotec Co., New Delhi
**Correspondence to:** Dr P. Kar, MD. DM. Professor of Medicine Maulana Azad Medical College, New Delhi-110002, India. pkar@vsnl.com
**Telephone:** +91-11-26889271 **Fax:** +91-11-23230132
**Received:** 2002-03-19 **Accepted:** 2002-05-10

## Abstract

**AIM:** The study was initiated to evaluate the reactogenicity and immunogenicity of a recombinant hepatitis B vaccine in 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 antibody) 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 GMT³ 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) hyporesponders (anti-HBs titers <10-99 mIU/ml) and 52.9 % (54/102) were responders (anti-HBs titers >100 IU/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 mIU/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 anti-HBs 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.

Das K, Gupta RK, Kumar V, Kar P. Immunogenicity and reactogenicity of a recombinant hepatitis B vaccine in subjects over age of forty years and response of a booster dose among nonresponders. *World J Gastroenterol* 2003; 9(5): 1132-1134
http://www.wjgnet.com/1007-9327/9/1132.htm

## INTRODUCTION

Hepatitis B infection is a major public health problem worldwide due to its long-term sequalae 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 intermdiate zone of HBV prevalence, and with a carrier rate of 4.7 %[1,2] has a 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[4-7]. The safety profile of the recombinant vaccine has been very good[8]. 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[9]. 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.

## 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 mg 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).

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 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 titres 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 ¼ (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) | | | |
|---|---|---|---|---|
| | 40 - 49 | 50 - 59 | > 60 | Total |
| Male | 52 (76.5%) | 13 (19.1%) | 3 (4.4%) | 68 |
| Mean GMT | 136.0 | 105.9 | 107.5 | |
| Female | 30 (91.1%) | 2 (5.8%) | 1 (2.9%) | 33 |
| Mean GMT | 145.4 | 177.6 | 41.56 | |

## 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[4,8,10-13], 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[23-25]. Most studies in literature have found a variable response rate of 40-60 %[28-30] to booster dose vaccination among nonresponders. Our study suggests a 100 % seroprotection rate after a single booster dose that is higher than most reports in the literature. One of the reasons for higher rate of seroprotection 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 % seroprotection 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.

## ACKNOWLEDGEMENT

We wish to thank Sanjay Singh and Abhijit Kumar of Panacea Biotec for extending co-operation and providing us the vaccine for the clinical trial.

## REFERENCES

1 **Thyagarajan SP**, Jayaram S, Mohanavalli B. Prevelance of HBV in the general population of India. In: Sarin SK, Singal AK (eds). Hepatitis B in India: Problems and prevention. *CBS publishers, New Delhi, India* 1996: 5-15
2 **John TJ**, Abraham P. Hepatitis B in India: A review of disease epidemiology. *Indian Pediatr* 2001; **38**: 1318-1325
3 **Chen CJ**, You SL, Lin LH, Hsu WL, Yang YW. Cancer Epidemiology and control in Taiwan: a brief review. *Jpn J Clin Oncol* 2002; **32** (Suppl): S66-81
4 **Arslanoglu I**, Cetin B, Isguven P, Karavus M. Anti-HBs response to Standard Hepatitis B vaccination in children and adolescents with diabetes mellitus. *J Pediatr Endocrinol Metab* 2002; **15**: 389-395
5 **Cook IF**, Murtagh J. Comparative immunogenicity of hepatitis B vaccine administered into the ventrogluteal area and anterolateral thigh in infants. *J Paediatr Child Health* 2002; **38**: 393-396
6 **Abraham B**, Baine Y, De-Clercq N, Tordeur E, Gerard PP, Manovriez PL, Parenti DL. Magnitude and quality of antibody response to a combination hepatitis A and hepatitis B vaccine. *Antiviral Res* 2002; **53**: 63-73

7 **Cassidy WM**. Adolescent hepatitis B vaccination. A review. *Minerva Pediatr* 2001; **53**: 559-566

8 **Elkayam O**, Yaron M, Caspi D. Safety and efficacy of vaccination against hepatitis B in patients with rheumatoid arthritis. *Ann Rheum Dis* 2002; **61**: 623-625

9 **Leroux-Roels G**, Cao T, De Knibber A, Meuleman P, Roobrouck A, Farhoudi A, Vanlandschoot P, Desombere I. Prevention of hepatitis B infections: vaccination and its limitations. *Acta Clin Belg* 2001; **56**: 209-219

10 **National Health and Medical Research Council**. The Australian Immunization Handbook. Australian Government publication Service (AGPS). *Canberra* 2000

11 **Leroy V**, Bourliere M, Durand M, Abergel A, Tran A, Baud M, Botta-Fridlund D, Gerolami A, Ouzan D, Halfon P, Zarski JP. The antibody response to hepatitis B vaccination is negatively influenced by the hepatitis C virus viral load in patients with chronic hepatitis C: a case control study. *Eur J Gastroenterol & Hepatol* 2002; **14**: 485-489

12 **Frcicioglu C**, Mikla S, Midilli K, Aydin A, Cam H, Ergin S. Reduced immune response to hepatitis B vaccine in children with insulin dependent dibetes. *Acta Paediatr Jpn* 1995; **37**: 687-690

13 **Bouter KP**, Diepersloot RJ, Wismans PJ, Gmelig Meyling FH, Hoekstra JB, Heijtink RA, van Hattum J. Humoral response to a Yeast-derived hepatitis B vaccine in patients with type 1 diabetes mellitus. *Diabet Med* 1992; **9**: 66-69

14 **Oguz Y**, Doganci L, Vural A. Seroconversion rates of two different doses of Hepatitis B vaccine in Turkish haemodialysis patients. *Cent Eur J Public Health* 2001; **9**: 44-45

15 **Tele SA**, Martins RM, Lopes CL, dos Santos Carneiro MA, Souza KP, Yoshida CF. Immunogenicity of a recombinant hepatitis B vaccine (Eurax B) in heamodialysis patients and staff. *Eur J Epidemiol* 2001; **17**: 145-149

16 **Desombere I**, Willems A, Zeroux-Roels G. Respause to hepatitis B vaccine: multiple HLA genes are involved. *Tissue Antigens* 1998; **51**: 593-604

17 **Lango-Warensjo A**, Cardell K, Lindblom B. Haptotypes comprising subtypes of the DQBI* 06 allele direct the antibody response after immunization with hepatitis B surface antigen. *Tissue Antigens* 1998; **52**: 374-380

18 **Caillat-Zucman S**, Gimenez JJ, Wambergue R, Albouze G, Lebkiri B, Naret C, Moynot A, Jungers P, Bach JF. Distinct HLA class II alleles determine antibody response to vaccination with hepatitis B surface antigen. *Kidney Int* 1998; **53**: 1626-1630

19 **Durupinar B**, Okten G. HLA Tissue types in non-responders to hepatitis B vaccine. *Indian J Pediatr* 1996; **63**: 369-373

20 **Looney RJ**, Hasan MS, Coffin D, Campbell D, Falsey AR, Kolassa J, Agosti JM, Abraham GN, Evans TG. Hepatitis B Immunization of healthy elderly adults: relationship between naïve CD4+ T Cells and primary immune response and evaluation of GM-CSF as an adjuvant. *J Clin Immunol* 2001; **21**: 30-36

21 **Bennett RG**, Powers DC, Remsburg RE, Scheve A, Clements ML. Hepatitis B virus vaccination for older adults. *J Am Geriatr Soc* 1996; **44**: 699-703

22 **Murhekar MV**, Murhekar KM, Arankalle VA, Sehgal SC. Immune response to an indigenously developed hepatitis-B (Shanvac-B) vaccine in a tribal community of India. *Vaccine* 2002; **20**: 3431-3435

23 **Zannolli R**, Morgese G. Hepatitis B vaccine: current issues. *Ann Pharmacother* 1997; **31**: 1059-1067

24 **Wismans P**, van Huttum J, Stelling T, Poel J, de Gast GC. Effect of Supplementary vaccination in healthy non-responders to hepatitis B vaccination. *Hepatogastroenterology* 1998; **35**: 78-79

25 **Clemens R**, Sanger R, Kruppenbacher J, Hobel W, Stanbury W, Bock HL, Jilg W. Booster immunization of low- and non-responders after a standard three dose hepatitis B vaccine schedule-results of a post marketing surveillance. *Vaccine* 1997; **15**: 349-352


**Edited by** Zhang JZ