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An open study to assess the safety and efficacy of Heprovac-B vaccine 10 mcg-dose for adults

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Short Report

An open study to assess the safety and efficacy of Heprovac-B vaccine 10 mcg-dose for adults

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Abstract

Heprovac B is a novel recombinant vaccine There are many vaccines available in Pakistani market but Heprovac B claims to be immunogenic even at 10 meg dose.Aim of the study is to determine whether using 10 meg of Heprovac B vaccine is safe and effective in producing sufficient immunity in Pakistani population. One hundred and twenty five subjects, who fulfilled the Inclusion criteria, were enrolled for the study. Heprovac B was administered in a three-dose regimen given at 0, 1 and 6 months and adverse events were recorded. Immunogenicity was tested by measuring hepatitis B surface antibody one month after each dose received.One month after the 3rd dose 98.7% of the subjects were found to be seroprotected with geometric mean titer of 488.83 mIU/1 after the third dose. Heprovac B, vaccine was well tolerated with minimal reported adverse events. It is safe and 10mcg is immunogenic in producing antibodies in Pakistani population against Hepatitis B virus.

Introduction

Hepatitis B virus infection is a major healthcare issue that affects children and adults worldwide. Long term infection can lead to chronic hepatitis, cirrhosis and primary hepatocellular carcinoma.[1] In Pakistan, Hepatitis B is one of the major causes of chronic liver disease and hepatocellular carcinoma. In Pakistan, the estimate is 4.5 million carriers, with a carrier rate of 3-4%.[2]

Since, there is no definite treatment available yet, great emphasis is being placed on its prevention through immunization.[3] Currently there are yeast derived vaccines present in Pakistan. The immunogenicity of these vaccines has been subjected to intense study since their birth.

There are three forms of HBsAg that are expressed in the hepatitis B vaccine, namely the major form consisting of the S protein alone, the large form containing the preS1 - preS2 - S components and a middle form containing pre S2 - S components. The presence of these conforms to the Immunogenicity of the vaccine.[4] The yeast cell recombinant vaccines contain only the major form i.e. only protein S; hence chances of failure of sero-conversion in these vaccines does exist.

The CHO cell derived vaccine, on the other hand,

contains all the three forms of HBsAg and therefore is highly immunogenic as compared to the plasma or yeast recombinant vaccines. Several studies conducted in adults, children and neonates showed that this vaccine is highly immunogenic and safe.[5-8]

Heprovac B (Recombinant Transgenic CHO Cell produce Hepatitis B Vaccine) is a non infectious subunit viral vaccine consisting of major protein of surface antigen (HBsAg) of HBV produced by a transgenic CHO cell line, which has been transfected by a recombinant plasmid containing a portion and been cloned. The Heprovac B is produced from cell cultures of Genetic Research Laboratory of Institute of Virology of Chinese Academy of Preventive Medicine.

The aim of this study was to determine whether the vaccination for hepatitis B using 10 mcg of CHO derived Heprovac B vaccine is able to produce sufficient immunity in Pakistani population.

Subjects, Methods and Results

This study was performed at a settlement in rural Sindh, near Hyderabad at Matiyari Sugar Mills, Matiyari . The trial was conducted under the ICH, GCP rules and the protocol was approved by the ethics review committee of the Aga Khan University Hospital, Karachi. After informed consent was obtained, blood samples were taken from each individual aged between 20 and 60 years, irrespective of gender. Initial HBsAg and HBsAb screening was done using EIA Abbott kit at Aga Khan Laboratories. Titers were expressed as milli international units per litre (mIU/L). A total of 125 subjects, who were negative for both HBsAb and HBsAg were enrolled in the study. Those subjects who had previous history of vaccination for hepatitis B and those found positive for HBsAb and HBsAg were excluded from the study. All these selected subjects were given 10 mcg of Heprovac B vaccine intramuscularly in the deltoid region at the classical 0, 1, and 6 months schedule. Blood sample were collected prior to the 2nd and 3rd and at 7th month to see the antibody response. The main outcome was the development of seroprotective levels of HBsAb in serum. HBsAb > 10 mIU/L was considered as serprotection. Safety was assessed in all the subjects by monitoring for 30 minutes after injection and local and systemic reactions for three days after each injection were reported. They were also asked to record any adverse events and illness that required medical attention between day three after vaccination and the next visit. Statistical analysis was preformed using SPSS version 11.

A total of 222 patients were screened out, of which 97 were excluded due to presence of positive results for HBsAb or HBsAg or both. One hundred and twenty five subjects with a mean age of 33.73 ± 10.33 years received a 10mcg dose for Heprovac-B vaccine at 0, 1 and 6 months. Antibodies titers were checked after one month of each dose. Twenty four subjects withdrew their consent after the screening. One hundred and one subjects received the first dose, 83 received the second dose and only 77 subjects completed the study. Of all the 77 subjects vaccinated, antibodies were successfully produced in 98.71% subjects while 1.29% did not produce the required antibodies.

In all these vaccinated subjects, ≥ 10 mIU/L antibodies were produced in 21.78% subjects after the first dose, 68.67% after the second dose and 98.7% after the third dose with 1.29% producing less than 10 mIU/L and none produced antibodies after the third dose. Antibody levels were divided into 5 categories i.e. levels of less than 10 mIU, 10-100 mIU, 100-1000 mIU, over 1000 mIU and no antibodies formed.

Adverse events reported were mild local reactions lasting for a day after vaccination and consisting mainly of pain upon pressure and movement. No serious adverse events were experienced.

The Geometric mean of antibodies was 57.06 mIU/L after the 1st dose, 119.41 mIU/L after the 2nd dose and 488.83 mIU/L after the 3rd dose as shown in Figure-1.

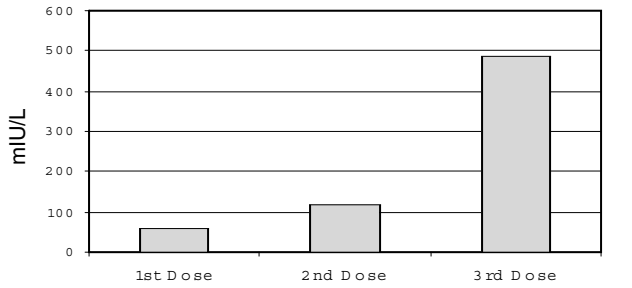

Figure 1. GMT of Antibodies.

The present study corroborates previous data showing that a new recombinant hepatitis B virus vaccine that contains the S-protein component of the HBV surface together with the Pre-S1 and Pre-S2 is more immunogenic. Several studies have been carried out in mice neonates and children, as well as in adults.[5,8] While the exact reason for the improved immunogenicity of CHO derived Hepatitis B vaccine are not completely understood, it is probably the result of the spherical structure obtained by producing the vaccine in an animal derived cell line (CHO) and from the presence of the Pre-S1 and Pre-S2 proteins on the surface of the vaccine particle.[6] The importance of Pre-S domains in the immunogenicity of HBV and the beneficial effect of an anti-Pre-S response in protective immunity has recently gained wide acceptance.[7]

Previously in a similar study, conducted in Karachi, with the same vaccine, where the 0-1-6 months schedule with 10 mcg was used in healthy individuals, an overall seroprotection rate of 27.2% was obtained at day 30 after the first dose, 72.8% after the second dose, 94.9% one month after the third dose and 1.3% produced less than 10IU and 3.8% not producing antibodies after the third dose.9 Our results, are consistent with these findings as shown in Figure 2. Drug A being the drug used in this study. The overall successful immunization was evident by the production of adequate HBsAb titers (98.7%) after the third dose of the vaccine. This figure is close to and slightly better than that of a previous study from PMRC, Karachi, Pakistan[9] using a dosage schedule similar to our study.

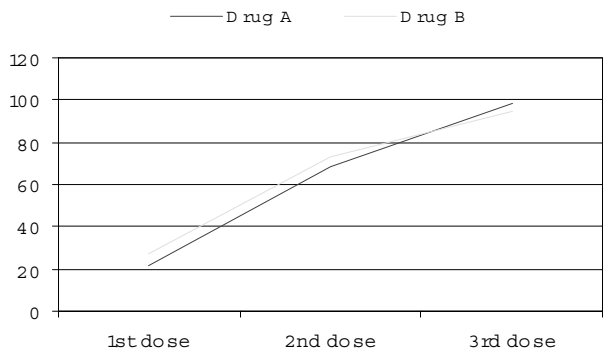

Figure 2. Efficacy comparison of hepatitis B vaccines used in two different studies (Drug A: used in this study. Drug B: used in study from PMRC, Karachi, Pakistan)

In conclusion Heprovac B, a novel recombinant DNA, CHO derived vaccine was well tolerated with minimal reported adverse events, all of which subsided rapidly. It is safe and 10mcg is immunogenic in producing antibodies in Pakistani population against Hepatitis B virus.

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References

1. Beasley RP, Lin CC. Hepatoma risk among HbsAg carriers. Am J Epidemiol 1978;108:247-50.
2. Abbas Z, Jafri W, Shah SHA, Khokhar N, Zuberi SJ and Members of the Consensus Panel, PGS Consensus Statement on management of Hepatitis B Virus Infection-2003. J Pak Med Assoc 2004; 54: 150-58.
3. Maynard JE. Hepatitis B: global importance and need for control; Vaccine. 1990;8 Suppl:S18-20.
4. Shouval D, Ilan Y, Adler R, Deepen R, Gerlich WH. Improved Immunogenicity in mice of a recombinant hepatitis B vaccine containing Pre-S1 and Pre-S2 antigens in Hbs patticles [Abstract]. J Hepatol 1991:S71.
5. Koren R, Yap I, Guan R, Lolekha S, Hourvitz A, Roash Z, et al. Safety, tolerability and immunogenicity in adults and children of a mammalian cell-derived recombinant hepatitis B vaccine, containing S, Pre-S and Pre-S . In: Rizetto M, Purcell RH, Gerin JL, Verme G, editors. Viral Hepatitis and Liver Disease. Proceedings of the IX Triennial International Symposium on Viral Hepatitis and Liver Disease. Turin: Edizioni Minerva Medica 1998; pp.970-3.
6. Raz R, Dagan R, Gallil A, Brill G, Kassis I, Koren R. Safety and immunogenicity of a novel mammalian cell-derived recombinant hepatitis B vaccine containing Pre-S1 and Pre-S2 antigens in children. Vaccine 1996, 3:207-11.
7. Yerushalmi B, Raz R, Blondheim O, Shumov E, Koren R, Dagan R. Safety and immunogenicity of a novel mammalian cell-derived recombinant hepatitis B vaccine containing Pre-S1 and Pre-S2 antigens in neonates. Pediatr Infect Dis 1997, 16:587-92.
8. Hourvitz A, Mosseri R, Solomon A, Yehezkelli, Y, Atsmon J, Danon YL, et al. Reactogenicity and immunogenicity of a new recombinant hepatitis B vaccine containing Pre S antigens: a preliminary report. J Viral Hepatitis 1996, 3:37-42.
9. Qureshi H. "Efficacy of Low dose CHO Cell derived Hepatitis B Vaccine in Children and Adults". JPMA; 2002, 52: 128.