Original Article

IMMUNOGENICITY AND ECONOMIC EVALUATION OF DIFFERENT RECOMBINANT HEPATITIS–B VACCINES IN DIFFERENT DOSAGES, SCHEDULES, AND ROUTES OF ADMINISTRATION

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ABSTRACT

Objective: To measure the immunogenic response produced by recombinant DNA derived vaccines in different dosages, schedules, and routes of administration. Another objective was to evaluate the minimum dosage and compliant schedule of recombinant DNA derived vaccine required to produce effective immune response and its economic evaluation in the adult population.

Methodology: Five hundred fifty eight healthcare workers in the age group of 20-50 years from Military Hospital Rawalpindi, Pakistan and other sister institutions were enrolled. Two hundred fifty eight were excluded due to serological evidence of HBV infection. Remaining three hundred were divided into five groups each having sixty volunteers with equal male to female ratio and age groups 20-29,30-39, 40-50. First four groups were injected with Heberbiovac vaccine and last group-V was given inj. Engerix–B. In Heberbiovac arm: Group-I received standard dose of 20µg at standard schedule of zero, one and six months intramuscularly. In Group-II, dose was reduced to half (10µg) intramuscularly. Group-III was given only two standard doses of 20µg at zero and one month interval intramuscularly and Group-IV received intradermal dose of 3µg at zero, one & six months. Group-V was given Engerix –B in standard dosage & schedule, (i.e., 20µg at zero, one and 6 months). Immunogenic response was measured in all the groups eight weeks after the last dose. Response was measured with MEIA/IMX system by ABBOTT.

Results: Both the vaccines were equally immunogenic but higher titers of Anti HBs was achieved with Heberbiovac. In Heberbiovac arm of study, seroprotection rate was 96.36% in Group-I, in Group-II it was 94.64%, in Group-III 95% and in intradermal group 98.14%. In Engerix –B group it was 92%.

Conclusion: Two doses/Half dose schedule/intradermal route of 3µg of Inj. Heberbiovac is equipotent to that of standard dose/schedule of Inj. Heberbiovac or Inj. Engerix–B in terms of seroprotection rate achieved.

KEYWORDS: Recombinant hepatitis–B vaccine, Immunogenicity.

Pak J Med Sci October - December 2008 (Part-II) Vol. 24 No. 6 833-837

How to cite this article:

Mumtaz B, Siddiq M. Immunogenicity and Economic Evaluation of Different Recombinant Hepatitis–B Vaccines in Different Dosages, Schedules, and routes of Administration. Pak J Med Sci 2008;24(6):833-37.

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* Received for Publication: August 20, 2008
* 1st Revision Received: October 27, 2008
* 2nd Revision Received: November 3, 2008
* Final Revision Accepted: November 13, 2008

INTRODUCTION

Hepatitis B is a major public health problem all over the world. More than two thousand million people have been infected by Hepatitis B virus, out of which more than four hundred million are chronic carriers resulting in significant morbidity and mortality.[1,2] Approximately

two thirds of Hepatitis B carriers live in third world countries.[2] In Pakistan carrier rate of Hepatitis B virus infection is 5-10%, many of these patients would end up in chronic hepatitis, cirrhosis, end stage liver disease and hepatocellular carcinoma.[3,4]

The World Health Organization has recommended the massive use of vaccines with the long-term aim of eradicating the virus and its associated diseases.[5-7] The immunogenicity of Hepatitis B vaccines has been the subject of study since their introduction. Both the plasma derived and recombinant DNA derived vaccines have been shown to provide seroprotection in more than 90% of cases.[8-14] High cost is an important reason for non-vaccination and non-compliance to vaccination schedule is also a factor which is more common in developing countries.[15,16] Two-dose vaccination schedule would not only reduce cost but also improve compliance.[17] Reducing the dose to half would also add to reduction in costs of vaccination, provided it does not effect immunogenicity in terms of antibody titres and seroprotection rate.[17,18] Using intradermal route with reduced dose can be an alternative way of reducing the cost during mass vaccination.[19-21] Immunogenicity among recombinant vaccines is different primarily due to differences in strain source, production and purification protocols.[11,22,23] A vaccine produced in recombinant *Pichia pastoris* yeast *(HEBERBIOVAC HB)* has been shown to be more immunogenic than other yeast species as measured by the seroprotection rates and geometric mean anti-HBs titers.[24] Therefore this vaccine was selected for testing with two shots or reduced dose immunogenicity trial.

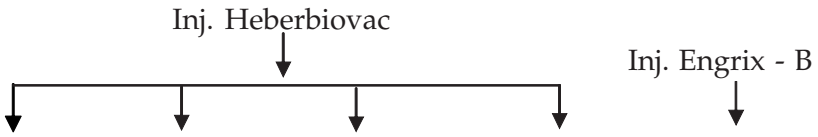
The objective of this study was to test whether low dose / two-dose schedule could render an adequate seroprotection rate in healthy individuals.

METHODOLOGY

After excluding those with evidence of HBV infection, three hundreds adults were included in this single blind, comparative analytical study. Healthy adults between the age group of 20-50 years with no degenerative, metabolic, proliferative or infectious disease were selected. Written informed consent was taken from all the study participants. Subjects previously immunized against hepatitis–B or suffering from hepatitis-B infection were excluded by testing serology for HBsAg, Anti- HBs and Anti- HBc. Pregnant or lactating women, those with diabetes mellitus, tuberculosis, chronic liver disease or any other chronic debilitating diseases were also excluded.

This study was conducted at Military Hospital Rawalpindi. Health care workers from Armed Forces Institute of Cardiology, Combined Military Hospital Rawalpindi were also enrolled. Study population (300) was divided into five groups having 60 participants each with equal male to female ratio and age groups of 20-29, 30-39 and 40-50 years respectively with 10 males and 10 females in each group. First four groups were injected with Inj. Heberbiovac while last Group-V was given Inj. Engerix-B in standard dosage (20µg) with schedule of zero, one & six months. In Heberbiovac arm, group-I was vaccinated with standard dose and schedule, while group-II was given half dose of (10µg) and in Group-III, (20µg) was given at zero and one month interval. Group-IV received intradermal Injection of (3µg) at zero, one and six months (Fig-1). The immunogenic response was measured in terms of antibodies titers (Anti HBs) eight weeks after the last dose and the results were compared (Table-I). All the tests were done using third generation micro particle immunoassay (MEIA)/IMX system by ABBOTT.

The efficacy of Heberbiovac vaccine was simultaneously compared with immunogenic response produced by *ENGRIX B* in standard dosage schedule of (20mg) at zero, one & six months interval. The test of significance was applied on the seroprotection rate in between all these groups to see the efficacy of low dose/ schedule/3µg intradermal route as compared to the standard regimen (Table-I).



	Group-I	*Group-II*	*Group-III*	*Group-IV*	*Group-V*
Dose	20µg	10µg	20µg	3µg	20µg
Schedule (months)	0,1,6	0,1,6	0,1	0,1,6	0,1,6
Route	I/M	I/M	I/M	I/D	I/M

IM = Intramuscular ID = Intradermal

Fig-1: Dosage, schedules and route of administration of vaccines.

RESULTS

Five hundred fifty eight healthcare workers were enrolled. Two hundred fifty eight subjects were excluded from the study due to serological evidence of HBV infection (HBsAg positive =18, HBcAb+= 158, HBsAb+=62). Thus a total of three hundred eligible subjects were studied. However, 25 subjects were lost to follow up (Group-I & II lost 5 and 4 respectively; Group-IV & V lost six and ten respectively). Therefore, 275 subjects were evaluated for their immunogenic response. Anti HBs titers of more than 10 mIU/ml is considered as optimum seroprotection as a standard.

In Heberbiovac group, the Group-I achieved 96.36% seroprotection rate in Group-II it was 94.64%, in Group-III 95% and in intradermal group 98.14%. In Engerix –B group it was 92%. These results were subjected to Chi square test in SPSS version 10, the pearson chi square value was 2.385 with degree of freedom being 04 and P value of (0.665). This shows no significant loss in terms of seroprotection achieved by all the groups (Table-I).

DISCUSSION

Since treatment of Hepatitis B is quite expensive, emphasis is placed on prevention through immunization. The immunogenicity of HB vaccines has been the subject of intense study since their introduction. Both plasma derived and recombinant DNA-derived vaccines have been shown to provide seroprotection in more than 90% of healthy adult or infant recipients.[8-14] These vaccines have good safety profile as well.[25,26]

Commonly recommended schedules comprise three vaccine injections. However, some people receive incomplete vaccination due to lack of information or motivation, high cost and long vaccination schedules irrespective of vaccine quality.[15] This is practiced even more often in developing countries.[16] Two dose vaccination schedules would not only reduce cost but also improve compliance. Since shorter course has proved to be effective as regard immunogenicity (antibody titers) and seroprotection rate, this could also prove use-

Table- I: Antibody titre and seroprotection rates

Groups	*No Response*	*Hypo response (Anti HBs Ab titers <10 mIU/ml)*	*Seroprotection (Anti HBsAb titers > 10mIU/ml)*	*Total Patients*	*Percentage Response*
Group-I	1	1	53	55	96.36%
Group-II	2	1	53	56	94.64%
Group-III	1	2	57	60	95%
Group-IV	0	1	53	54	98.14%
Group-V	1	3	46	50	92%

Pearson chi square value was 2.385 with degree of freedom being 04 and P value of (0.665).This shows no significant loss in terms of seroprotection achieved by all the groups.

ful for low dose vaccine administered intradermaly.[17,18] In previous clinical studies with recombinant *Pichia pastoris* yeast *(HEBERBIOVAC HB)*, antibody production and serum titers continue to increase after the first month following immunization.[13]

Results showed that vaccine administered in low dose/schedule was equally effective as that of standard dose & schedule. Two dose schedule proved as immunogenic as three dose regimen but it also ensured better compliance as there was no loss of number of participants in this study group. Intradermal route of administration with 1/7th of standard dose gave good results. Intradermal route is traditionally also thought to be immunogenic in non responders & in patients on hemodialysis.[27-29] In one study, for example, 50 hemodialysis patients were revaccinated either intradermaly or intramuscularly with a total dose of 80µg of recombinant vaccine. Seroconversion rates at 20 months were much higher in the group vaccinated intradermaly (54 versus 0 percent).[30]

A meta-analysis of 12 studies concluded that initial response was more with the intradermal administration.[31] Intradermal inoculation appears to be more immunogenic than intramuscular injections, but is technically more difficult to administer. [27-29] A two dose regimen or a half dose regimen has the advantage of reducing the total cost and resources required for vaccination program. This could also prove useful for low dose vaccine administration. In a double blind randomized prospective study by Piacio Pedroso Flaquet et al, Heberbiovac was used in a dose of 5, 10, 15 and 20µg in healthy subjects between 17-34 years of age at zero, one, two & twelve months, antibody levels were measured at 60, 90 and 365 days after the first dose. It demonstrated high immunogenicity. Protective mean antibody titer was present in a dose less than that recommended by the manufacturer.[32] In another study by Gonzalez–Griego MJ et al, two doses of vaccines administered at zero and two months in adults aged 18-23 proved as immunogenic as three doses.[33] Study by Hugh P.levaux et al, in three different settings; public schools, public health clinics and private sector settings in the United States showed that two dose schedules provide high probability of adolescents achieving seroprotection.[17] When the long term consequences of hepatitis B virus infection are considered, it would be cost effective as compared with three dose regimen in all settings which would result in significant cost savings.

Results of another study by William M. Cassidy and colleagues showed that a two dose regimen of Recombivax HB is also immunogenic and induces immunologic memory as effectively as the recommended three dose regimen.[18] A regimen of two (20µg) doses may be of significant benefit among those who are non compliant or deviate from vaccination schedule. As such for poor countries where cost is a major obstacle against mass vaccination, low dose / Intradermal route is a good option. This can have a huge financial and compliance impact, particularly in the developing world.

CONCLUSION

Both the vaccines are equally immunogenic but higher titers of anti-HBs is achieved with Heberbiovac. Two dose schedule can be recommended in young adults as there is no significant difference in the antibody levels and a very high compliance. Half the dose (10µg) of Heberbiovac is as effective as the standard dose (20µg) but titers are low. Intradermal route with 3µg is more immunogenic hence, it could be a useful option where cost is a serious issue and in patients who do not respond to intramuscular route but technically it is more difficult to administer.

ACKNOWLEDGMENT

This trial was co-sponsored by Macter Pakistan and Heber Biotec Havana. The authors also wish to acknowledge the hard work done by the paramedics and technicians.

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