ORIGINAL ARTICLE

Response of Preterm Infants of Mothers Who Are Chronic Carriers of Both HBsAg and HBeAg to Pre-S2 Containing Hepatitis B Vaccine (TGP 943) - A Preliminary Report

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ABSTRACT This study aimed to examine the immunogenecity and protective efficacy of a pre-S2 containing hepatitis B vaccine (TGP 943, Takada, Japan) in 9 preterm infants. A control group of preterm infants were given plasma derived hepatitis B vaccine (Korean Green Cross, Korea). All these preterm infants were born to both HBsAG and HBeAg posistive mothers and born in central General Hospital Sanglah Denpasar from January 3, 1992 to October 30, 1992. The gestational ages were 35-37 weeks and birth weights were 2000-2500 grams. The difference of the anti preS2 antibody between two groups of preterm infants was evident at month 6. Anti-HBs antibody response was almost same in the two groups of preterm infants. None in preterm infants in this study became positive for HBsAg during follow-up for at least 6 months. 2 of 8 preterm infants in control group become positive for HBsAg during follow up for at least 6 months. Our study demonstrated a better anti pre-S2 antibody response and also comparable anti-Hbs antibody response in preterms infants vaccinated with a pre-S2 containing hepatitis B vaccine, compared with those with conventional plasma-derived vaccine. **[Paediatr Indones 1995; 35:211-215]**

Introduction

Hepatitis B vaccination and HB immunoglobulin prevent perinatal transmission of hepatitis B in normal term infants born to mothers who are chronic carriers of hepatitis B surface antigen.[1] The Committee on Infection Disease of the American Academy of Pediatrics stated in 1991 that "data on the effectiveness of HB vaccine are not available for infants with birth weight less than 2000 grams".[2] WHO has concluded that the simplest

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and most effective strategy for the control and eventual eradication of HBV in Southeast Asia and the Pacific would be to immunize all newborns with hepatitis B vaccine.[3]

Several workers have recently reported achieving approximately 90% efficacy in preventing the carrier state in infants of HBeAg positive mothers by use of recombinant HB vaccine without HBIg.[4] Plasma-derived HB vaccine alone have an efficacy of about 75% in preventing the development of carrier state if given soon after birth.[4] However, the vaccine is not efficient in the immunocompromised,[5,6] genetic non-responders, in elderly,[5] in preterm infants[2] and in a second serotype of hepatitis B virus (Hepatitis B escape mutant).[5] Vaccine containing pre-S sequences was as efficient in preventing the HBV carrier state in children born to HBsAg and HBeAg positive mothers, as the vaccine containing only S protein combined with HBIg.[6] HB vaccine that contain the pre-S1 and/or pre-S2 viral proteins may induce seroconversion in some of the small group of corresponds to current vaccines, which appear to approach 100% in individuals who seroconvert.[4] It is possible that pre-S1 or pre-S2 antibodies may improve duration of long-term immunity.[7,8]

This study aimed to study the immunogenecity and protective efficacy of pre-S2 containing hepatitis vaccine (TGP-943) in preterm infants.

Methods

A total of 4500 pregnant women attending the maternity clinic at Central General Hospital Sanglah Denpasar (Bali, Indonesia) were systematically screened (last trimester of pregnancy) for the presence of HBsAg. Of 440 preterm infants recruited at birth, sixteen healthy preterm infants who were born to both HBsAg and HBeAg positive mothers between 3 January 1992 and 30 October 1992 and born in central General Hospital Sanglah Denpasar were eligible for inclusion in this trial. The gestational ages were 35 to 37 weeks and birth weight 2000 g to 2500 g. The sex ratio was male / female =1:1. A vaccination schedule of 3 doses of 10 μg of pre-S2 containing hepatitis B vaccine (TGP943) were given to 9 preterm infants and 10 μg conventional plasma derived hepatitis vaccine (Korean Green Cross Korea) were given to 8 preterm infants at 0, 1, and 2 months. Venous blood samples were drawn from umbilical cord blood at 1, 6, and 12 months to determine HBsAg, anti-Hbs antibody, e antigen and anti-e antibody; They were assayed by using RPHA, ELISA, PHA. Anti pre-S2 antibody was determined using enzyme linked immunosorbentassay (ELISA) with a synthetic pre-S2 peptide as a solid antigen pre-S2-containing vaccine was developed by Takeda Chemical Industries using recombinant yeast and designated TGP-943. Conventional plasma derived hepatitis B vaccine was produced by Korea Green Cross, Korea. Injection was given in the infant's anterolateral thigh.

Results

After screening pregnant women for hepatitis B markers, 16 preterm infants born to s+/e+ were enrolled in the study. The gestational age was 35-37 weeks and birth weight 2000-2500 grams. Immunogenicity of the vaccine for preterm infants of s+/e+ and s+/e- mothers is shown in Tables 1 and 2.

Table 1. Anti pre-S2 antibodies ELISA optical densities (x1000)

Vaccine	Cord	Month 1	Month 6	Month 12
TGP	n = 0	n = 5 21	n = 3 435	n = 1 327
Plasma	n = 2 17	n = 4 34	n = 4 32	n = 1 17

The difference in anti-pre-S2 antibody titer between the two groups of preterm infants was most evident at month 6.

Table 2. Anti HBs antibody titers

Vaccine	Cord	Month 1	Month 6	Month 12
TGP		n = 2 2.5	n = 2 4	n = 3 6
Plasma	n = 0	n = 2 1	n = 2 2.5	n = 2 4

Anti-Hbs antibody response was almost the same in the two groups. The protective efficacy of the vaccine for premature infants of s+/e- and s+/e+ mothers is shown in Figure 1.

None of the preterm infants vaccinated with pre-S2 containing vaccine became positive for HBsAg during follow-up for at least 6 months. Two of 8 preterm infants vaccinated with conventional plasma derived vaccine followed from birth to 6 months become positive for HBsAg and this two preterm infants were born to antigen positive mothers. One of control group was HBsAg positive in umbilical cord and then became negative for HBsAg this difference is apparently suggesting the superiority of TGP over conventional plasma-derived hepatitis B vaccine.

Discussion

The Committee on Infection Diseases of the American Academy of Pediatrics stated in 1991 that "data on the effectiveness of HB vaccine are not available for infants with birth weights less than 200 grams".[2]

Seroconversion after administration of HB vaccine is influenced by a number of variables.[2] Injection of vaccine into subcutaneous fat, older age, and impaired immune status are all associated with lower seroconversion rate.[2] Prematurity was also associated with a lower response to HB vaccine.[2] Carman et al. discovered a second serotype of hepatitis B virus (Hepatitis B Escape Mutant) that this not protected by the hepatitis B vaccine.[5] Infants born to mothers who are chronic HBs-Ag carries, especially mothers who are also positive for HBeAg, are at very high risk of becoming chronically infected carries themselves.[1]

The difference in anti-pre-S2 antibody titer between the groups of preterm infants in our study was most evident at month 6. Anti-HBs antibody response was almost same in the groups of preterm infants. None of preterm infants vaccinated with pre-S2 containing hepatitis B vaccine became positive for HBsAg

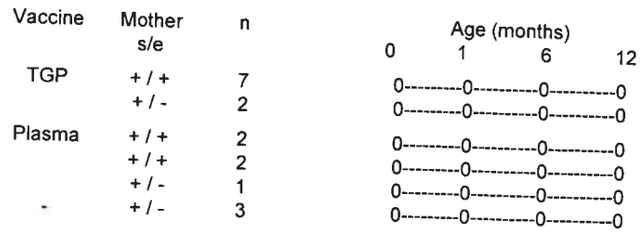

Figure 1. Protective efficacy PreS2 containing vaccine and conventional plasma derived vaccine as determined by HBsAg status of preterm infants:O=-HbsAg; O=+HBsAg.

during follow-up for at least 6 months, and 6 of them were born to e antigen-positive mother. Two subjects in the control group became positive for HBsAg during follow-up at least 6 months and were born to e antigen-positive mothers. This difference suggests the superiority of TGP over conventional plasma derived hepatitis B vaccine, and is also suggestive of the advantageous addition of the pre-S2 portion into the vaccine to prevent mother-to-infant transmission of HBV.

Vaccine based solely on S protein may have great disadvantage.[6] However, other vaccine containing the additional protein compose of the HBV envelope appear to be more efficacious.[6] A vaccine containing pre-S2 sequences was as efficient in preventing the HBV carrier state in children born to hepatitis B surface antigen (HBsAg) and hepatitis-B e-antigen (HBeAg) positive mothers, as the vaccine containing only S protein combined with HBIg.[6] Since combined use of both a vaccine and HBIg is rather expensive, a vaccine is needed which will be efficient without the use of HBIg.[6] It appears likely that such a vaccine can be developed if other protein components of the HBV envelope or corresponding synthetic peptide analogues are incorporated into the vaccine.[6]

The presence of pre-S2 sequences in a vaccine is expected to (a) decrease that genetic restriction of the immune response to the vaccine,[6] (b) enhance the antibody response to S protein,[6,8] and (c) results in a broader and stronger immune response, leading to improved protection against HBV infection.[4,9]

If further studies involving larger number of neonates can confirm these results, active vaccination with pre-S containing hepatitis B vaccine can be considered as a reliable alternative to passive and active-passive immunization for the protection of neonates at risk for hepatitis B infection. WHO has concluded that the simplest and most effective strategy for the control and eventual eradication of HBV in Southeast Asia and Pacific would be to immunize all newborn with hepatitis B vaccine.

Conclusion

Our study demonstrates a better anti-pre-S2 response and also comparable anti-HBS antibody response in preterm infants vaccinated with a pre-S2 containing hepatitis B vaccine, compared with those conventional plasma-derived vaccine. This finding suggests the use of pre-S2 in preventing mother-to-infant transmission of HBV even without the use of HBIG.

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References

1. Poovorawan Y, Sanpavat S, Pongpunlert W, et al. Comparison of recombinant DNA hepatitis B vaccine alone or in combination with hepatitis B immune globulin for the prevention of perinatal acquisition of hepatitis B carriage. Vaccine 1990; 8: 56-9.
2. Yu LL, Tam AYC, Ng KW, et al. Response of preterm infants to hepatitis B vaccine. J Pediatr 1992; 121:962-5.
3. WHO Report. Meeting of task force on hepatitis B. Regional office for the Western Pacific Manila, Philippines, March, 1984.
4. Kane Mark A. John Clements, Dale Hu. The global control of hepatitis B. In: Assessment and management of risks associated v ith hepatitis B. Effectiveness of intervention. Philadelphia: Hanley & Belfus, 1990;75-92.
5. Hilleman Maurice R. The vaccine solution to the problem of human hepatitis B and it sequelae. In: Assessment and management of risks associated with hepatitis B: Effectiveness of intervention. Philadelphia: Hanley & Belfus, Inc., 1990; 19-31.
6. Neurat AR, Kent SBH, Strick N, Parker A. The biological role of pre-S sequances for vaccine design. Asian Symposium on Strategies for Large Scale Hepatitis B Immunization, Hongkong, June 12-13, 1986.
7. Adamowicz P, Cuoursaget P, Mazert MC, Goudeau A, Lagarde D, Girard M. Pre-S antigenity and preS immunogenecity of a hepatitis B vaccine. Asian Symposium on Strategies for Large Scale Hepatitis B Immunization, Hongkong, June 12-13, 1986.
8. Tiollais P, Michel ML, MIllich DR, Chisari FV. Synthesis in chocells of Hepatitis B surface antigen particles containing the pre-S2 region expression product. Asian Symposium on Strategies for Large Scale Hepatitis B Immunization, Hongkong, June 12-13, 1986.
9. El Goulin. Importance of the production process for the preparation of a safe hepatitis B vaccine of optimal antigenic quality. Asian Symposium on Strategies for Large Scale Hepatitis B Immunization, Hongkong, June 12-13, 1986.