Asian Pacific Journal of Allergy and Immunology (1988) 6 : 107-110

Hepatitis B Immunization in High Risk Neonates Born from HBsAg and HBeAg Positive Mothers : Comparison of Standard and Low Dose Regimens.

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SUMMARY **A reduced dose of plasma derived hepatitis B vaccine (Hevac B®) was tested for efficacy in the prevention of perinatal hepatitis B virus (HBV) transmission in high risk neonates born from e-antigen positive HBsAg carrier mothers. Forty newborn infants born of these mothers were given hepatitis B immune globulin (HBIG) 100 IU intramuscularly immediately after birth, combined with either standard or reduced doses of HBV vaccine. The infants were divided into two groups of 20 infants each. The standard dose of HBV vaccine (5 μg) was given to group I, while infants in group II received reduced dose (2 μg) at birth and at 1, 2 and 12 months of age. There was no statistically significant difference in the efficacy and antibody responses of these two combined prophylaxis regimens. The protective efficacy rate of HBV vaccine was found to be 94.0 and 93.2 percent in group I and group II, respectively. At twelve months of age, the anti-HBs seroconversion rates were 80.0 percent in group I and 86.7 percent in group II, with geometric mean titres of 84.57 mIU/ml and 78.56 mIU/ml, in group I and group II, respectively. One month after a booster at one year of age, anti-HBs could be detected in 86.7 percent of the infants in both groups. The geometric mean titres were 429.04 and 664.81 mIU/ml, in group I and group II, respectively. Anti-PreS2 antibody was detected in high titre as early as 4 months after the first dose of HBV vaccine, with a geometric mean titre of 116.30 mIU/ml and 107.97 mIU/ml, in group I and group II, respectively. It is concluded that a reduced dose (2 μg) of plasma derived hepatitis B vaccine (Hevac B®) could be used as effectively as the standard dose (5 μg) in the prevention of perinatal HBV transmission in high risk neonates born from e-antigen positive HBsAg carrier mothers.**

In Thailand, hepatitis B virus (HBV) is transmitted from asymptomatic carrier mothers to their babies, especially when mothers are seropositive for hepatitis B e-antigen.[1-3] Our previous studies have demonstrated the safety, immunogenicity, and efficacy of hepatitis B immunoglobulin (Gamma protect®) and hepatitis B virus vaccine (Hevac B®) in prevention of the HBsAg carrier state in newborn infants of mothers who are chronic carriers of HBsAg and HBeAg.[4] As the cost of the vaccine is still high, it is not applicable for wide spread use in an immunization schedule in endemic areas of developing countries such as Thailand. The purpose of the present study was to investigate the efficacy of a low dose regimen of plasma derived hepatitis B vaccine (Hevac B® , 2 μg) combined with hepatitis B immunoglobulin (HBIG Gamma protect®) as compared to the standard dose of vaccine (5 μg) for the prevention of transmission of hepatitis B virus (HBV) in high risk neonates born from chronic carrier mothers of HBsAg and HBeAg.

PATIENTS AND METHODS

Between June 1986 and December 1986 a total of 9,600 Thai pregnant women were screened for HBsAg and HBeAg by the reversed passive hemagglutination method (RPHA). Of these, 538 (5.6 percent) were HBsAg positive, and of these, HBeAg was detected in 42.6 percent. New born infants in HBsAg carrier mothers who were also HBeAg positive were randomly assigned to two groups (20 cases in each group) for the prevention of perinatal HBV transmission. Group I was treated with HBIG 100 IU (Gamma protect®

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0.5 ml) intramuscularly in conjunction with 5 μg of HBV vaccine (Hevac B®) intramuscularly at birth, followed by Hevac B 5 μg at 1, 2 and 12 months of age. Group II was treated with HBIG 100 IU (Gamma protect®) intramuscularly in conjunction with 2 μg of HBV vaccine (Hevac B®) intramuscularly at birth, followed by Hevac B 2 μg at 1, 2 and 12 months of age. The follow up for clinical evidence of hepatitis or complications and for serological tests of HBsAg, HBeAg, anti-HBs, anti-PreS2 and anti-HBe was carried at 0, 4, 6, 12 and 13 months of age. Among the forty infants in this clinical trial, 82.5 percent had perfect follow up records.

Laboratory tests were performed as follows : the initial screening tests of pregnant women for HBsAg and HBeAg were done by the reversed passive hemagglutination method (RPHA) as previously described.[5] The blood specimens from the HBsAg carrier mothers who were also HBeAg positive were confirmed once again for HBsAg and HBeAg after delivery. Infant blood specimens were tested for HBsAg and anti-HBs by enzyme linked immunosorbent assay (ELISA, Behring Enzygnost HBsAg test kit). The anti-PreS2 test was performed by the ELISA method using a solid phase coated with 31 amino acid peptide (subtype adwz, Pasteur Vaccines, Laboratorie de controle). Anti-HBc was determined by the passive hemagglutination test (PHA, Core cell Green Cross, Osaka) and by enzyme linked immunosorbent assay (Corzyme Abbott) in specimens obstained at 6 and 12 months of age. HBeAg was determined by the RPHA method (anti-e cell Green Cross, Osaka) only for HBsAg positive specimens.

RESULTS

Forty infants born of HBsAg carrier and HBeAg positive mothers received combined prophylaxis with HBIG and different doses of HBV vaccine. Eighteen out of 20 cases in group I (receiving 5 μg HBV vaccine) and 15 out of 20 cases in group II (receiving 2 μg of HBV vaccine) were perfectly followed up to the age of one year. Neither local nor systemic reactions were observed after immunization with HBIG and hepatitis B vaccine. Persistent HBs-antigenemia with positive HBeAg was found for one case in each group (5.5 and 6.7 percent in group I and group II, respectively). The protective efficacy rate of the HBV vaccine was found to be 94.0 and 93.2 percent in group I and group II, respectively (Table 1). There was no statistically significant difference ($p > 0.05$) between the efficacy of HBV vaccine in these two groups. At twelve months of age, anti-HBe could be detected in 90.0 percent of infants in group I and 86.7 percent in group II with geometric mean titres of 84.57 mIU/ml and 78.56 mIU/ml in group I and group II, respectively (Tables 1 and 2). The differences between these two groups were not statistically significant ($p > 0.05$). The details of the serial determinations of anti-HBs are shown in Table 3. One month after booster with Hevac B 5 μg (group I) and 2 μg (group II) at one year of age, the anti-HBs could be detected in 86.7 percent of the infants in both groups, with geometric mean titres of 429.04 and 664.81 mIU/ml in group I and group II, respectively.

At four months of age, anti-PreS2 could be detected in 68.8 percent of the infants in gorup I and 29.4 percent in group II with geometric mean titres of 116.36 mIU/ml and 107.97 mIU/ml, respectively (Tables 2 and 3). One month after booster at 1 year of age with Hevac B 5 μg (group I) and 2 μg (group II), anti-Pre S2 could be detected in 66.7 percent and 93.3 percent of infants with geometric mean titers of 172.54

Table 1. The efficacy of a reduced dose (2 μg/ of hepatitis B vaccine (group II) as compared to the standard dose (5 μg, group I) in prevention of perinatal HBV transmission.

Study group	No. of Infants	Efficacy (%)	Geometric mean titre (mIU/ml) of anti–HBs	
			Age 12 mon	Age 13 mon*
I (5 μg)	20	94.0	84.57 (n = 12)	429.04 (n = 13)
II (2 μg)	20	93.2	78.56 (n = 13)	664.81 (n = 13)

*After a booster at one year of age

Table 2. Seroconversion rate in high risk neonates receiving at birth HBIG 100 IU and a standard dose (5 μg, group I) or a reduced dose (2 μg, group II) of hepatitis B vaccine at birth and at 1, 2 and 12 months of age.

Study group	Seroconversion rate (%)							
	Age 4 mon		Age 6 mon		Age 12 mon		Age 13 mon	
	Anti–HBs	Anti–PreS2	Anti–HBs	Anti–PreS2	Anti–HBs	Anti–PreS2	Anti–HBs	Anti–PreS2
I (5 μg) (n=20)	83.3 (n=15)	68.8 (n=11)	76.5 (n=13)	71.4 (n=11)	80.0 (n=12)	69.2 (n=9)	86.7 (n=13)	66.7 (n=8)
II (2 μg) (n=20)	57.9 (n=15)	29.4 (n=5)	57.9 (n=11)	37.5 (n=6)	86.7 (n=13)	70.6 (n=12)	86.7 (n=13)	93.3 (n=14)

Table 3. Antibody response (anti–HBs and anti–Pre S2) following immunization at birth with HBIG 100 IU and a standard dose (5 μg, group I) or a reduced dose (2 μg, group II) of hepatitis B vaccine at birth and at 1, 2 and 12 months of age.

Study group	Geometric mean titres (mIU/ml) of anti–HBs and anti–Pre S2							
	Age 4 mon		Age 6 mon		Age 12 mon		Age 13 mon	
	Anti–HBs	Anti–PreS2	Anti–HBs	Anti–PreS2	Anti–HBs	Anti–PreS2	Anti–HBs	Anti–PreS2
I (5 μg) (n=20)	48.47 (n=15)	116.36 (n=11)	78.06 (n=13)	80.10 (n=11)	84.57 (n=12)	91.99 (n=9)	429.04 (n=13)	172.54 (n=8)
II (2 μg) (n=20)	71.01 (n=15)	107.97 (n=5)	103.04 (n=11)	112.33 (n=6)	78.56 (n=13)	160.24 (n=12)	664.81 (n=13)	228.35 (n=14)

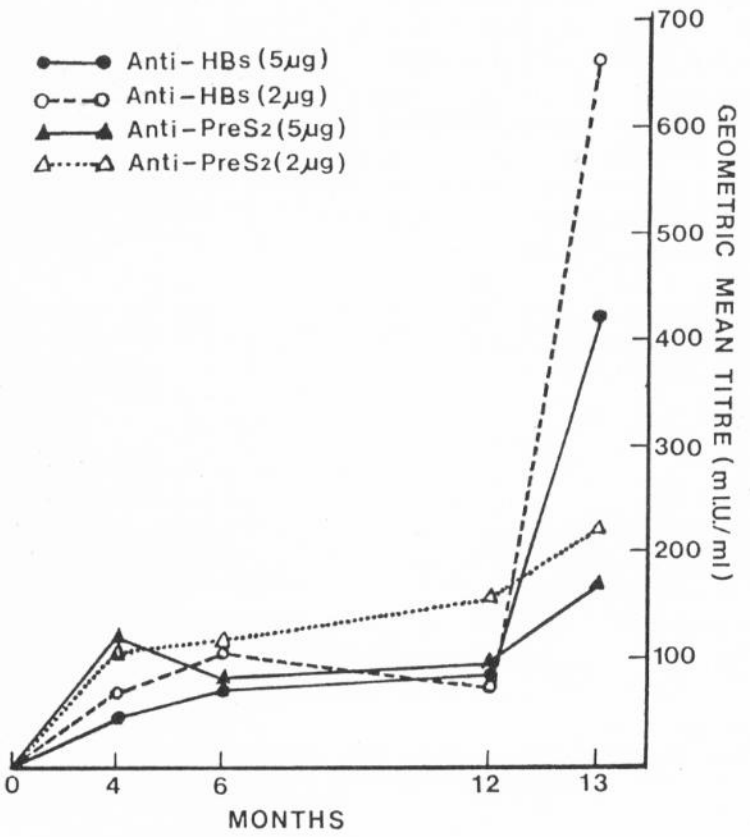

Fig. 1 Comparison of the antibody response following immunization with the standard dose (5 μg) or a reduced dose (2 μg) of hepatitis B vaccine.

mIU/ml and 228.35 mIU/ml, respectively (Tables 2 and 3). A comparison of the mean titres of anti-HBs and anti-PreS2 antibody responses between the two groups is shown in Fig. 1.

At six months of age, anti-HBc could be detected in 83.3 percent and 70.0 percent of infants in group I and group II, respectively. The incidence of anti-HBc at twelve months of age was found to be 85.7 percent in group I and 71.4 percent in group II.

DISCUSSION

Chronic carriers of HBsAg are at high risk of chronic liver diseases, cirrhosis and ultimately primary hepatocellular carcinoma later in life.[6,7] In areas of hyperendemicity such as Thailand, perinatal transmission of HBV from e-antigen positive HBsAg carrier mothers to their babies is the most important cause of chronic HBsAg carriers.[1,8] Thus, interruption of perinatal HBV transmission from HBsAg carrier mothers to infants is extremely important, especially in high risk neonates born from e-antigen positive HBsAg carrier mothers. Our previous studies and several other studies have shown that combined prophylaxis with hepatitis B immunoglobulin (HBIG) and hepatitis B vaccine immediately after birth followed by two doses of hepatitis B vaccine is highly effective in preventing transmission of HBV from HBeAg positive carrier mothers to their infants.[4,9,10] A protective efficacy rate of 90-100 percent could be obtained from this combined prophylaxis schedule in high risk newborn infants similar to those obtained by immunization in older children and adults.[11] However, the high cost and limitted availability of the plasma-derived hepatitis B vaccine is still a major obstacle to its widespread use in people living in endemic areas of HBV infection. Many developing countries in endemic areas simply cannot afford the cost of a national program for hepatitis B immunization in all high risk neonates, unless the current prices of vaccines are significantly lowered. A reduction in vaccine dosage, without loss in protective efficacy is one way to overcome the problem of high vaccination cost and to promote availability for broader use. The present study shows that a low 2 μg dose of hepatitis B vaccine (Hevac B®) is as effective as the standard 5 μg dose in prevention of

perinatal transmission of HBV from e-antigen positive HBsAg carrier mothers. There was no statistically significant difference in the protective efficacy rate between infants receiving the standard dose (5 μg) and reduced dose (2 μg) of vaccine. The protective efficacy rates were similar to those found for previous studies in Taiwan and Hong Kong.[9,10,12] Moreover, 86 percent of the infants immunized with the low dose regimen still had significantly high titres of anti-HBs at twelve months of age, and this was similar to the titre for infants who received the standard dose of hepatitis B vaccine. The anti-HBs antibody in these infants was maintained at a highly protective level until the administration of the booster injection at one year of age. Following booster immunization, similar and very good anti-HBs and anti-PreS2 antibody responses were also observed in both groups. This resulted in a steep increase (4-6 times) of anti-HBs even in infants receiving the low dose vaccine regimen. Therefore, the booster injection at one year of age was efficient and was necessary to sustain long lasting immunity for the prevention of further horizontal HBV transmission later in life. This study provides evidence that immune responses to a reduced dose of hepatitis B vaccine are satisfactory in high risk newborn infants. It is concluded that a reduced dose (2 μg) of the plasma derived hepatitis B vaccine (Hevac B®) could be used as effectively as the standard dose (5 μg) in the prevention of vertical HBV transmission in high risk neonates born from e-antigen positive HBsAg carrier mothers. This approach would certainly reduce the cost of hepatitis B immunization to prevent perinatal HBV transmission and it could be applied economically for the national program of HBV transmission control. Long term follow up for the efficacy of this immunization regimen is in progress.

Another interesting finding in this study was the observation of an early rise of anti-PreS2 antibody within 4 months after administration of the first dose of hepatitis B vaccine. The mean anti-PreS2 titre was well above the protective level and was comparable in both groups. It was higher than the anti-HBs titre at the same time. A rapid increase in anti-PreS2 antibody could beneficial for high risk infants by eliminating persisting HBV and by preventing the attack and replication of HBV in hepatocytes. This being so, the use of HBIG immediately after birth in high risk neonates might not be necessary and we might be able to use hepatitis B vaccine alone to induce the early production of anti-PreS2 antibody and to prevent perinatal HBV transmission. This approach would further reduce the cost of immunization and it should be further investigated.

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