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Efficacy of Hepatitis-B Immunoglobulin and Hepatitis-B Vaccine in Prevention of the HBsAg Carrier State in Newborn Infants of Mothers Who are Chronic Carriers of HBsAg and HBeAg

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SUMMARY **Combined prophylaxis of perinatal transmission of hepatitis B virus (HBV) with hepatitis-B immunoglobulin (HBIG) and hepatitis-B vaccine was investigated in 40 infants born to HBeAg positive carrier mothers. The efficacy of two combined prophylaxis schedules was compared to 78 similar infants in the control group receiving no treatment, by following the HBV markers at regular intervals up to one year of age. In both schedules, the HBIG and HBV vaccine were given at birth, followed by HBV vaccine given at 30 days and 60 days (group I) or 180 days (group II) of age. The incidence of persistent HBsAg carrier in infants born to HBeAg positive carrier mothers was significantly reduced from 92.6 percent at one year of age in the control group to zero percent (group I) and 11.5 percent (group II) in the treated groups. There was no statistical significant difference in the efficacy of these two combined prophylaxis schedules. HBIG given at birth did not interfere with infant immune response to the hepatitis B vaccine. At twelve months of age, anti-HBs could be detected in 77.8 percent of infants in group I and 89.5 percent in group II with mean titre of 621.4 and 1148.0 in group I and group II respectively. It was concluded that combined prophylaxis with HBIG and hepatitis-B vaccine immediately after birth is the best method for prevention of HBV perinatal transmission from HBeAg positive carrier mothers to their infants.**

In areas of hyperendemicity such as Asia and Oceania, hepatitis B virus (HBV) is transmitted from asymtomatic carrier mothers to their babies, especially when mothers are seropositive for hepatitis Be antigen.[1,2] Almost all of such babies become persistent carriers and constitute a reservior of HBV for further spread in the community. In order to eradicate HBV, measures must be taken to interrupt the mother-to-baby transmission. We have recently shown that either hepatitis-B immunoglobulin (HBIG) or hepatitis-B vaccine alone administered to infants from HBsAg carrier with HBeAg positive mothers immediately after birth reduces the number of perinatally infected carriers by about 75 and 65 percent respectively.[3,4] It was the purpose of the present study to compare the efficacy of combined hepatitis-B immunoglobulin and hepatitis-B vaccine administered to infants from HBsAg carrier with HBeAg positive mothers to those obtained by using isolated hepatitis-B immunoglobulin or hepatitis-B vaccine in the previous reports. It was found that the combined prophylaxis with HBIG and hepatitis-B vaccine almost completely prevent HBV transmission from carrier mothers to their infants.

SUBJECTS AND METHODS

Between November 1984 and June 1985, a total of 11,375 Thai pregnant women were screened for HBsAg and HBeAg by reversed passive haemagglutination method (RPHA). Of these, 666 (5.9 percent) were HBsAg positive of whom HBeAg was detected in 39.2 percent. Newborn infants of the HBsAg carrier mothers with HBeAg positivity were randomly assigned to two groups (20 cases in each group) for prevention of perinatal HBV transmission. Group I was treated with HBIG 200 I.U. (Gamma-protect)® intramuscularly in conjunction with 5 μg of HBV vaccine (Hevac B)® intramuscularly at birth and Hevac B 5 μg at 30 and 60 days. Group II was treated with HBIG 100 I.U. (Hepatect)® intravenously in conjunction with 10 μg HBV vaccine (HB vax)® intramuscularly at birth and 10 μg HB vax intramuscularly at 30 and 180 days. The follow up for clinical evidence of hepatitis or complications and serological

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tests for HBsAg, HBeAg, anti-HBs and anti-HBc were done at 0,2,4,6 and 12 months of age. Among the forty infants in this clinical trial, 92.5 percent had a perfect follow up record. The control group consisted of 78 infants born to HBsAg positive mothers receiving no prophylaxis. The HBsAg carrier status in these infants were determined at 0,2,4,6 and 12 months of age, similar to the treated group.

Laboratory tests were performed as follows: initial screening of pregnant women for HBsAg and HBeAg by reversed passive haemagglutination method (RPHA) as previously described.[1] The blood specimens from the HBsAg carrier mothers with HBeAg positive were confirmed for HBsAg and HBeAg once more after delivery. Infant specimens were tested for HBsAg and anti-HBs by enzyme linked immunosorbent assay (Behring Enzygnost HBsAg test kit). Anti-HBc was done in specimens obtained at 6 and 12 months by passive haemagglutination test (PHA, Core-cell Green Cross, Osaka) and enzyme linked immunosorbent assay (Corzyme Abbott). HBeAg was done by RPHA (anti-e cell Green Cross, Osaka) only in the HBsAg positive specimens.

RESULTS

As shown in Table 1, the vertical transmission of HBsAg from the carrier mothers to their infants in the control group causing a persistent HBsAg carrier state was found only in HBeAg positive carrier mothers (92.6 percent) but not in HBeAg negative mothers. This difference is statistically significant ($p < 0.01$).

Among 40 infants born from HBsAg carrier with HBeAg positive mothers who received combined prophylaxis, 18 out of 20 cases in group I

Table 1 Perinatal transmission of hepatitis B surface antigen (HBsAg) and e-antigen (HBeAg) from HBsAg carrier mothers to children at one year of age in the control group (78 infants).

Group of mothers with			No. tested	No. positive in infants		
HBsAg	HBeAg	Anti-HBe		HBsAg	HBeAg	anti-HBe
+	+	−	27	25 (92.6%)	20 (74.1%)	0
+	−	+	19	0	0	0
+	−	−	32	0	0	0
	Total		78	25 (32.1%)	20 (25.6%)	0

Table 2 Incidence of HBsAg carriers in infants following immunisation with HBIG 200 I.U. intramuscularly in conjunction with 5 μg HBV vaccine (Hevac B) intramuscularly at birth and Hevac B 5 μg at 30 and 60 days (Group I) as compared to HBIG 100 I.U. intravenously in conjunction with 10 μg HBV vaccine (HB vax) intramuscularly at birth and HB vax 10 μg intramuscularly at 30 and 180 days.

Group	No. of infants	No. of HBsAg positive in infants at the age of				
		0 mo.	2 mo	4 mo	6 mo	12 mo
I	20	0	0	0	0	0
II	20	0	1 (5.0%)	2 (10.0%)	2 (10.0%)	2 (10.5%)*
Total	40	0	1 (2.5%)	2 (8.1%)	2 (8.1%)	2 (8.1%)

*Two infants who became HBsAg carriers had positive HBeAg. The difference of persistent HBsAg in infants of two groups is not statistically significant by Fisher exact probability test ($p > 0.05$).

and 19 out of 20 cases in group II could be perfectly followed to the age of one year. Neither local nor systemic reactions were observed after immunisation with hepatitis-B immunoglobulin and hepatitis-B vaccine. No persistent HBsAg antigenaemia developed in group I but in group II persistent HBsAg antigenaemia with positive HBeAg was found in 2 out of 19 cases (10.5 percent). There is no statistical significant difference ($p > 0.05$) between these two groups (Tab.2). The incidence and the mean titre of anti-HBs detected in infants following immunisation with HBIG and HBV vaccine are shown in Table 3. Anti-HBs could be detected in all infants in both groups at two months of age in low titre due to the residual HBIG given at birth, however, the mean titre of anti-HBs was increased progressively later on in both groups. At twelve months of age, anti-HBs could be detected in 77.8 percent of infants in group I and 89.5 percent in group II with the mean titre of 621.4 and 1148.0 in group I and group II respectively. These differences are not statistically significant ($p > 0.05$). The incidence of anti-HBc in infants at the ages of six and twelve months is shown in Table 4. Anti-HBc developed in 68.8 and 36.8 percent in group I and 76.5 percent and 5.9 percent of infants in group II at the ages of six and twelve months respectively.

DISCUSSION

Perinatal HBV infection often leads to HBsAg carrier state especially in infants born to HBeAg positive carrier mothers. Chronic carriers of HBsAg are at high risk of chronic liver diseases and ultimately cirrhosis and primary hepatocellular carcinoma later in life.[5,6] Thus, interruption of perinatal HBV transmission from HBsAg carrier

Table 3 Antibody response (anti-HBs) following immunisation with HBIG 200 I.U. intramuscularly in conjunction with 5 μg HBV vaccine (Hevac B) intramuscularly at birth and Hevac B 5 μg at 30 and 60 days (Group I) as compared with HBIG 100 I.U. intravenously in conjunction with 10 μg HBV vaccine (HB vax) intramuscularly at birth and HB vax 10 μg intramuscularly at 30 and 180 days (Group II).

Group	No. of infants	Percent of infants with rising anti-HBs at the age of				
		0 mo	2 mo	4 mo	6 mo	12 mo
I	20	-	100 (48.0)*	94.4 (117.0)	75.0 (266.7)	77.8 (621.4)
II	20	-	100 (33.3)	64.4 (500.0)	84.2 (702.7)	89.5 (1148.0)
Total	40	-	100.0	81.1	75.6	83.7

*( ) = mean anti-HBs titre in I.U. per litre.

Table 4 Prevalence of anti-HBc in non-HBsAg specimens of infants at the age of six and twelve months.

Group	No. tested	Percent of anti-HBc positive infants at the age of	
		6 mon.	12 mon.
I	19	68.8* (11/16)	36.8** (7/19)
II	17	76.5* (13/17)	5.9** (1/17)

*Statistically not significant by Chi-square test ($p > 0.05$).
**Statistically significant by Chi-square test ($p < 0.05$).

mothers with positive HBeAg to their infants is extremely important. This study showed clear cut evidence that combined prophylaxis given in good schedule and optimal time are highly effective in reducing the HBsAg carrier state in infants. The efficacy of 90-100 percent obtained from these two combined prophylaxis schedules in our study is similar to the previous study in Taiwan.[7] Immediate administration of HBIG is essential in the prevention of perinatal HBV infection suggesting that HBIG works initially by blocking or decreasing viral access to the liver. The efficacies of HBIG given intramuscularly and intravenously are almost the same. The very high attack rates in untreated babies and the rapid onset of HBsAg appearance in the infants suggest high infectivity of the mothers during labour. Furthermore, the HBeAg positive mothers remain a high risk source of HBV for continuing exposure to their children. Most of the siblings of these infants were also HBsAg carriers with HBeAg positive. However, the result of our anti-HBs and anti-HBc study in the combined prophylaxis groups showed that the risk of continued exposure is not so high as we formerly though because almost all of the non-HBsAg infants born from HBeAg positive mothers have excellent natural and artificial immune responses (Tables 3 and 4). Both intramuscular and intravenous HBIG given in conjunction with HBV vaccine at birth did not interfere with the immune response to the HBV vaccine. The HBIG passively given by intravenous route disappears more rapidly from the serum than when it is given by intramuscular route. In Thailand, the cost of HBIG and HBV vaccine is still very high. Thus, for neonates born to HBsAg and HBeAg positive mothers, a combination of 0.5 ml HBIG in conjunction with HBV vaccine started at birth and followed by one or two doses of HBV vaccine is being studied as an alternative approach to prophylaxis. The efficacy of this approach will be disclosed by our study in Thai infants at the beginning of next year. We believed that the effective interruption of perinatal transmission of HBV from HBeAg positive carrier mothers to their infants will reduce the incidence of chronic HBsAg carrier status and hence the incidence of cirrhosis and primary hepatocellular carcinoma in the future.

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