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Original Article

Serologic status at 10 months of infants born to hepatitis B positive mothers given prophylaxis - A prospective cohort study

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ABSTRACT

Rationale: Perinatal exposure is the most common mode of transmission of hepatitis B (HB) infection in neonates. Prevention of perinatal transmission of HB is important to decrease overall carrier state. **Objectives:** To estimate the rate of HB carrier status among children born to HB surface antigen (HBsAg) positive mothers at 10 months of age measured by HBsAg status and to assess the efficacy of prophylaxis (HB vaccine [HBV] and HB immunoglobulin [HBIG] administration) as measured by the anti-HBs titer at 10th month of age. **Methodology:** This was a hospital based prospective cohort study of infants born to HBsAg positive mother between April 2008 and October 2008 with a follow-up at 6 weeks, 14 weeks, and 10 months of age. After informed consent from the parents, 0.5 ml of recombinant vaccine was given to all. HBIG was given to only those who could afford to buy it. At 6 and 14 weeks of age, 0.5 ml of recombinant vaccine was given according to the IAP immunization schedule along with other UIP vaccines to all neonates. At 10 months of age (plus 1 week), 69 infants completed 3 doses of HBV. Anti-HBs titer and HBsAg status were measured. Anti-HBs titer >100 IU/L was taken as a good responder. **Results:** Total 125 infants were initially recruited. All were vaccinated with HBV within 12 h of birth. HBIG was given to 96 infants (76.8%) and only 69 (55.2%) completed 3rd visit. Carrier state in infants born to HBsAg positive mothers at 10 months of age was 1/69 (1.44%). 43/69 (62.35%) had good antibody response out of which, 41 were given both HBV and HBIG. In those given only vaccine, 2/7 (28.55%) had good antibody response (p=0.02). **Conclusion:** Combined HB vaccine and immunoglobulin had a better antibody response in the study as reported earlier. The carrier state was 1.44%.

Key words: *Followup, Infant, HBsAg positive mother*

Hepatitis B (HB) is one of the most common and serious infectious diseases, and about 5% of the population of the world are chronic carriers of HB virus. Nearly 25% of all carriers develop serious liver diseases such as chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma [1]. In endemic areas of Africa and Asia, the epidemiological patterns differ from those seen in North America and Western Europe. In these regions, most infections occur in infants and children as a result of maternal-neonatal transmission or close childhood contact; although percutaneous exposure with contaminated needles or following unsafe injections is always a possibility in these countries [1]. With a prevalence of 2-7% HB surface antigen (HBsAg) seropositivity, India has an intermediate endemicity, and a projected burden of 50 million carriers, the 2nd largest in the world [2,3]. In India, the HBsAg prevalence rate among pregnant women varies between 0.9% and 11.2% [4-6]. Without immune prophylaxis, in mothers who are both HBsAg and Hepatitis B e antigen (HBeAg) positive, the risk for transmission to the baby is between 70% and 90% by 6 months of age, whereas in the case of mothers who are HBsAg positive, but HBsAg negative, it is <10% [7-10].

Perinatal exposure is the most common mode of transmission in neonates. More than 90% of infected infants become chronic carriers. Prevention of perinatal transmission of HB is important to decrease overall carrier state. The transmission of perinatal HB infection can be prevented in 70-95% of neonates born to HBsAg positive mothers by early active immunization and 85-95% by combined active and passive immunoprophylaxis.

Although the introduction of the birth dose of HB vaccine (HBV) will go a long way to reduce maternal-neonatal transmission, there needs to be a system in place to ensure universal screening during pregnancy, timely administration of the birth dose and tracking of babies exposed to HB. Awareness of the current recommendations for managing babies of mothers who are HB carriers is not universal, resulting in failure of follow-up, despite the serious long-term implications including development of hepatocellular carcinoma [11]. In this context,

this study attempts to estimate the rate of HB carrier status among infants born to positive mothers at 10 months of age by measuring serum HBsAg levels and to assess the efficacy of prophylaxis as measured by the anti-HBs antibody titers at 10 months of age.

METHODOLOGY

We recruited HBsAg positive mothers from the labor room and postnatal ward of SAT Hospital, Trivandrum, which is a tertiary care teaching hospital between 1st April and October 31st 2008 and had a prospective follow-up of the infants at 6 weeks, 14 weeks, and 10 months of age. All consecutive, live born neonates, born to HBsAg positive mothers were included in the study. Parents of neonates, recruited for the study, were counseled about the disease, need for post-exposure prophylaxis and follow-up. After obtaining informed consent from the parents, 0.5 ml of recombinant vaccine (Revac-b from Bharat Biotech-Hyderabad) was given intramuscularly into the right thigh within 12 h of birth from the hospital free of cost. HB immunoglobulin (HBIG) was given to only those who could afford to buy it. Hepatitis 100 IU (0.5 ml) from VHB Pharmaceuticals was given intramuscularly into the left thigh within 24 h of birth. Half-life of HBIG is 23.1±5.5 days. At 6 and 14 weeks of age, 0.5 ml of recombinant vaccine was given according to the IAP immunization schedule along with other UIP vaccines to all neonates. Three dose schedules were the protocol followed in our hospital.

At 10 months of age (or plus 1 week), informed consent for blood sample collection was obtained from the parents of the children. Blood samples were drawn after taking universal precautions. The sera were separated and stored at 20°C until tested. HyperCard "Sand which" immune assay kit (J Mitra and Co., Ltd., New Delhi) was used for HBsAg status determination and electro chemiluminescent immunoassay using ELECSYS 2010 system (Roche diagnostics GmbH, Mannheim, Germany) for the estimation of anti-HBs antibody titer. All tests were conducted in advanced clinical and research lab attached to the Medical College, Trivandrum. Infants with anti-HBs titer >100 IU/L were considered as good responders. If anti-HBs titer was <10 IU/L (nonresponder), the whole vaccine series was repeated by 0, 1, 6 schedule and post-vaccination serology was done after 2 months. If the anti-HBs titer was 10 to 100 IU/L (poor responder), 1 booster dose of HBV was given. Post-vaccination serology was done after 2 months. The study protocol was approved by the Institutional Ethics Committee.

Demographic details and follow-up information along with estimates of biochemical markers were collected in a case record format for each HBsAg positive mother-infant pair. Data entered into the Microsoft Excel 2003 and analyzed by SPSS 11.0 windows at clinical epidemiology research training center, medical college, Trivandrum. Independent sample t-test was used to compare continuous variables and Chi-square was used to compare discrete variables. For the comparison of anti-HBs titer in the vaccine alone group and vaccine plus HBIG combination group was done by Mann–Whitney test. Geometric mean titer was also calculated.

RESULTS

The total number of deliveries during the study period was 8365. There were 125 mothers who were HBsAg positive. This gives an estimated prevalence rate of HBsAg positivity in pregnant women at birth as 1.5%. Mean maternal age was 24.1±2.28 years. 60.8% of the mothers were primigravida and 16 (12.8%) mothers had a history of the previous abortions. 99/125 (79.2%) had vaginal deliveries. In 3 cases, husbands were HB carriers and none of them had given a history of transfusion of blood products. None of them had evidence of other reproductive tract infections. In 32 cases, HBsAg titer was measured; of which, 8 (25%) were HBsAg positive. Due to very small number, separate analysis of that subgroup was not done. Majority (119 [95.2%]) of them were term babies and 6 (4.8%) were preterm. Mean birth weight was 2.88±0.41 kg and all were exclusively breastfed till 6 months of age. The baseline characteristics are summarized in Table 1.

All 125 children were vaccinated with HBV within 12 h while HBIG was given to 96 infants (76.8%). Only 69 (55.2%) of the cohort completed 3rd visit as ours is a referral hospital where HBsAg positive mothers are being referred for the delivery. They go back to nearby hospital for vaccinations. Carrier state in infants born to HB positive mothers at 10 months based on HBsAg positivity was 1/69 (1.44%). 43/69 (62.35%) had good antibody response, and among them, 41 received HBV plus HBIG combination. Among 7 infants who received vaccine alone, 2 had good antibody response (p=0.02). Mean antibody titer in vaccine group (163.38) was significantly different from that of the combined group (443.14), (p=0.011). We compared geometric means also and in combined group, it was 164.02 while it was 9.75 in the vaccine group (p=0.01). The comparisons of risk are summarized in Tables 2 and 3.

Table 1: Baseline characteristics of HBV alone and HBV+HBIG combination groups

Variables	HBIG+HBV vaccine (n=96)	HBV vaccine alone (n=29)	Significance (p-value)
Male to female ratio	52:44	15:14	0.57
Urban:Rural	15:81	4:25	0.810
Mean maternal age (SD)	24.08 (2.31)	24.17 (2.25)	0.85
Primigravida: Others	62:34	14:15	0.118
Husband carrier	2	1	
Normal: Others	75:21	24:5	0.636
Mean baby weight	2.93 (0.409)	2.72 (0.372)	0.01
Term: Preterm	92:4	27:2	0.548

HBV: Hepatitis b vaccine, HBIG: Hepatitis b immunoglobulin, SD: Standard deviation

Table 2: Comparison of two groups based on anti-HBs titer at 10 months

Group	Nonresponder (%)	Poor responder (%)	Good responder (%)	p-value
Vaccine+HBIG	7 (11.29)	14 (22.58)	41 (66.12)	<0.002*
Vaccine alone	5 (71.42)	0	2 (28.5)	
Total	12 (17.39)	14 (20.28)	43 (62.315)	

*With continuity correction, HBs: Hepatitis b

Table 3: Risk estimates

Efficacy of intervention	Estimate (%)	95% Confidence limits (lower, upper)
Protective response in HBIG+HBV group (good+poor response)	88.71	78.19, 94.72
Protective response on HBV alone	28.57	7.564, 64.76
Risk ratio (protection)	3.105	0.9592, 10.05*
Risk difference	60.14	25.76, 94.52

*Just achieving significance at p=0.05

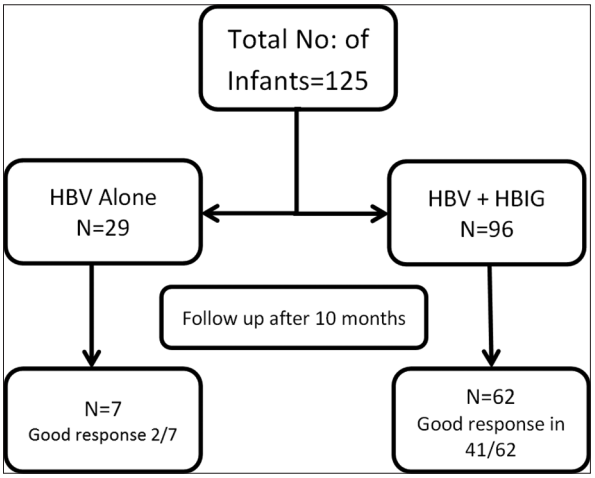

Figure 1: Follow-up details of the cohort

DISCUSSION

This study has highlighted the need for implementing an effective policy for the management and follow-up of neonates born to HBsAg positive mothers. It is reported that without prophylaxis, 40% of the infants born to HBsAg positive mothers will get infected [12]. In our study in which 69 out of 125 HBsAg positive mothers were followed up, 1 infant was HBsAg positive at 10 months which comes to an incidence of 1.5%. It is reported that despite newborn immunoprophylaxis, vertical transmission may still occur in 1-14% cases [13]. Thus, the incidence seen in our setting is at par with the reported literature. However, it is important to note that at the time of the study the use of HBIG was not available free of cost for the patients in the tertiary care setting itself and hence, some of the families could not afford it. Non-compliance to the follow-up visit could be attributed to ease of accessibility to immunization services in all areas in the state and availability of child health specialist everywhere. Families preferred to have postnatal visits at their residential areas.

The combination of HBV with HBIG has provided significant protective efficacy compared to the HBV alone group (relative risk=3.05). In 65.4% of the infants who had an adequate response, it could be attributed to the intervention alone. It is already established that the combined vaccine and immunoglobulin given at birth reduces the risk of transmission significantly. However, it is important to note that nearly 23% of those infants who received a combination of HBV and HBIG were found to be poor responders at 10 months necessitating additional booster dose. This highlights the need for proper follow-up and documentation of the cases. There is also the need to establish laboratory capacity for estimation of biomarkers free of cost. This study does have limitations with nearly 45% not completing the adequate follow-up. Furthermore, the loss to follow-up was significantly more in the vaccine alone group, and it is not possible to predict how this would have influenced the risk estimate.

CONCLUSION

Our study demonstrated an adequate response in infants provided with combination prophylaxis compared to vaccine alone and highlighted the possibility of poor responders. The possibility of poor response makes it imperative that the follow-up needs to be meticulous along with adequate awareness building for parents on the need for follow-up. Figure 1 shows the summary of the subjects followed up.

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