



The Effects of Anti-HBs Antibodies Passed through Transplacental Route on Immunization Induced by HBV Vaccine and Natural Course of Passively Transmitted HBs Antibodies

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Abstract

Introduction: Hepatitis B infection is an important infection that concerns public health. In this study, we aimed to evaluate whether anti-Hbs antibodies born from mothers who are immune to hepatitis B virus with natural or vaccination and passed from mother to baby transplacentally affect the natural course of these passive anti-HBs antibody titers.

Methods: In this study, 68 healthy term newborn babies were included. The immune status of the mothers of these newborn babies was evaluated. Babies were divided into three groups. Group 1, babies whose mothers were positive for AntiHBs antibody, anti-HBs titers were evaluated consecutively at 0, 1, 3, 6 and 8 months without HBV vaccine. In Group 2, babies whose mothers were positive for anti-HBs antibody were vaccinated with HBV vaccine at 0.1 and 6 months, and these babies were examined for anti-HBs titers at 0.1, 3, 6 and 8 months. In Group 3, babies whose mothers were negative of anti-HBs antibody were vaccinated with HBV vaccine at 0, 1 and 6 months, and babies were examined at 0.1, 3, 6 and 8 months.

Results: Group 1 consisted of 22 babies, Group 2 consisted of 24 babies and Group 3 consisted of 22 babies. Percentages of anti-HBs titers falling below <10 mIU/mL at 1, 3, 6 and 8 months were found to be 40.9%, 50%, 59.09%, and 100% of non-vaccinated babies whose mothers were positive for anti-HBs antibody.

Discussion and Conclusion: We found that the antibody response to HBV vaccine administered to infants with passive antibodies was similar to the antibody response in mothers vaccinated with their mothers HBsAg (-), anti-HBs (-), anti-HBcIgM (-) and the same vaccine calendar. Thus, it was found that anti-HBs antibodies that started this transplacental pathway did not affect the antibody response produced by the HBV vaccine administered at 0, 1 and 6 months.

Keywords: Anti-HBs; HBsAg; Hepatitis B vaccine.

Hepatitis B infection is a disease that has an important role in the etiology of chronic liver disease and hepatocellular carcinoma (HCC) seen in all regions of the world^[1]. In undeveloped countries, hepatitis B virus (HBV) infection is common; transmission is more vertical, high-risk groups are primarily newborns and children^[2, 3].

Turkey is located in the middle frequency band in the world in terms of the epidemiology of hepatitis B^[4, 5]. Approximately 1-1.5 million births are delivered annually in our country and an average of 100.000 HbsAg- positive mothers give births^[4-6]. This number is quite high. Concerning public health, these mothers and their children should be

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carefully monitored. Special training of horizontal and vertical transmission routes and taking necessary precautions are very important^[6, 7].

In this study, we aimed to evaluate whether or not anti-HBs antibodies transmitted from mothers who are naturally immune to hepatitis B virus or through immunization to their babies using transplacental route affect the immunity induced by HBV vaccine in newborn babies, and also the natural course of these passively transmitted anti-HBs antibody titers in vaccinated and unvaccinated newborn babies.

Materials and Methods

This study started after the approval of the ethics committee was obtained (No: 97-057). Sixty-eight healthy term newborns were included in this study. HBsAg, anti-HBs and anti-HBcIgM were evaluated to assess the natural or vaccine-related immune status of the mothers of all newborn babies included in this study. Anti-HBs titers of newborns were examined within the first postnatal 24 hours. Anti-HBs titers above >10 mIU/mL were evaluated as antibody positivity. Accordingly, newborn babies participating in this study were divided into three groups as follows:

Group 1 consisted of babies whose mothers were positive for anti-HBs antibody, anti-HBs titers of these babies were consecutively evaluated at 0, 1, 3, 6 and 8 months without immunization with HBV. Babies whose anti-HBs titers dropped below 10mIU/ml were excluded from this study and included in the routine Hepatitis B virus vaccination program.

Group 2 consisted of babies whose mothers were positive for the anti-HBs antibody. These babies were vaccinated with HBV vaccine at 0.1 and 6 months, and these babies were examined for anti-HBs titers at 0.1, 3, 6 and 8 months.

Group 3 consisted of babies whose mothers had HBsAg (-), anti-HBs (-), antiHBcIgM (-) were vaccinated with HBV vaccine at 0, 1 and 6 months, anti-HBs titers of these babies were evaluated at 0,1, 3, 6 and 8 months.

In this study, the recombinant HBV vaccine (Euvax-B) obtained from the Provincial Health Directorate was administered to the babies. Vaccines consisting of 10 ml vial were used within one day after opening the vials, and a cold chain procedure was observed. All infants were administered a 10 mcg/dose (0.5 ml) vaccine through the intramuscular route. Serum was separated after venous blood samples were taken from all cases and centrifuged. Serum samples were kept at -40 °C in the deep freeze until the day of analysis. This study was performed using Enzyme Immunoassay (EIA) method.

Statistical Methods

For statistical evaluation of the findings, complementary statistical methods were used (such as arithmetic mean and standard deviation). Since the distribution of our groups did not fit the normal distribution pattern, Kruskal-Wallis variance analysis was used to compare more than three groups, and Mann-Whitney U test was used in pairwise comparisons. The correlation coefficient between the groups was determined using Spearman's correlation analysis.

Results

A total of 68 healthy term newborn babies were included in this study. Mothers of 46 babies were either naturally immune or immunized with the hepatitis B virus. The mothers of the remaining 22 newborn babies were HBsAg (-), anti-HBs (-) and anti-HBcIgM (-). Anti-HBs titers of all newborns were examined in the first 24 hours after birth.

It was seen that these antibodies passed from mothers to their newborns in 99.8% of the cases through transplacental route. Group 1 comprised 22, Group 2, 24 and Group 3, 22 babies. Mean, maximum, and minimum anti-HBs values of the groups at 0, 1, 3, 6, 8 months are shown in Tables 1, 2 and 3. When the anti-HBs titers of the 22 babies in Group 1 were evaluated, anti-HBs titers below 10 mIU/mL were detected in 9 of the 22 babies (40.9%). Anti-HBs titers decreased below 10mIU/mL in 11 (50%) cases at the 3rd, in 13 (59.09%) cases at the 6th, and 22 cases (100%) at the 8th month.

Table 1. Anti-HBs (mIU/mL) values of Group 1 patients

Months	Cases (n)	Minimum-Maximum	Mean±SD
0	22	13.5-2895.0	464.5±752.1
1	22	0-1761.0	231.1±429.7
3	13	0-237.0	81.8±83.1
6	11	0-120.0	30.4±40.0
8	9	5.0-5.0	5.0±0.0

SD: Standard Deviation.

Table 2. Anti-HBs (mIU/mL) values of Group 2 patients

Months	Cases (n)	Minimum-Maximum	Mean±SD
0	24	10.1-3200.0	715.1±1017.6
1	24	0-2347.0	388.6±642.9
3	24	21.3-1476.0	494.9±403.4
6	24	35.6-3200.0	973.7±858.5
8	24	43.8-3200.0	1646.0±721.8

SD: Standard Deviation.

Table 3. Anti-HBs (mIU/mL) values of Group 3 patients

Months	Cases (n)	Minimum-Maximum	Mean±SD
1	22	6.5-32.0	14.0±6.9
3	22	51.3-608.0	229.1±171.3
6	22	170.0-2000.0	820.4±535.5
8	22	272.0-2000.0	1295.7±732.8

SD: Standard Deviation.

Intergroup comparison of the anti-HBs titers measured in months 0, 1, 3, 6, 8 is shown in Table 4. In the 1st month, antibody titers (Group 3) of babies without transplacentally transmitted antibodies and thus vaccinated were observed to be quite low compared to babies having transplacentally transmitted antibodies (Groups 2 and 3). When comparing the averages of anti-HBs (mIU/mL) titers in the third month between groups, it was found that there was a statistically significant difference between Groups 1 and 2 ($p=0.03$), but the mean anti-HBs (mIU/mL) titers of Group 3 did not differ significantly compared to Groups 1 and 2 ($p>0.05$). When comparing the averages of anti-HBs (mIU/mL) titers at 6th month, it was observed that these titers in Group 1 were statistically significantly lower than Groups 2 and 3 but without any difference between Groups 2 and 3. Finally, when mean values of anti-HBs (mIU/mL) titers at 8th month were compared between groups, similar results were obtained, as is the case with titers measures at the 6th month.

Discussion

Because of its chronicization fulminant course, vertical, and horizontal infectivity, being both an etiologic agent for hepatocellular carcinoma and a predisposing factor for delta infection, HBV infection is a critically important entity that threatens the health of the individual^[2, 8]. In Turkey, approximately 4 million people have been chronically infected with the hepatitis B virus (HBV)^[4, 5]. In our country, the etiological agent is HBV alone in 45% of pa-

tients with chronic hepatitis and in 35% of patients with liver cirrhosis^[4]. Each year, 12% of HBeAg-positive cases with chronic hepatitis progress to liver cirrhosis and 15-20% of anti-HBe-/HBV DNA-positive cases^[4]. Again, every year, 0.2-0.7% of cases with chronic hepatitis related to HBV progress to hepatocellular carcinoma^[9].

Short and long-term undesirable complications may develop as a result of infection^[10]. To keep HBV under control, precautionary strategies have been developed, such as screening the pregnancies of HBsAg before birth, to ensure the vaccination of the child to be born and other households, to include the Hepatitis B vaccine in the routine vaccination program, and to vaccinate every newborn, and adults at risk^[11, 12].

Taking up the virus during the neonatal period when the immune system is still immature, ends with chronicization in most cases^[5]. Approximately 30-50% of the babies born from asymptomatic HbsAg- positive mothers are seropositive when they reach their first year of age^[11]. HBV infections become chronic later on in 20-90% of the children, and 10-15% of the adults who take up HBV t^[5]. In conclusion, HBV infection is more important in children concerning chronicity and the consequent development of hepatocellular carcinoma. Taken the utmost importance of HBV infection in children into consideration, the World Health Organization stipulates since 1997 that every newborn all over the world should be immunized with HBV vaccine for protection from HBV infection.

HBV vaccine has to be administered to newborns since 1997. Today, in many countries, the HBV vaccine has entered the routine vaccination schedule.

In our study, it was observed that anti-HBs antibodies in the serums of vaccinated or natural immune mothers whose Anti-HBs titers were positive transmit to the baby through the transplacental route in 99.8% of the cases. In our study, anti-HBs titers were examined in the serums of 22 babies in Group 1 who did not receive the Hepatitis B vaccine at post-

Table 4. Intergroup comparisons of anti-HBs titers at 0., 1., 3., 6., 8. months

Anti-HBs	Group1	Group2	Group3	Group 1 vs. Group 2 P	Group1 vs. Group 3 P	Group 2 vs. Group 3 P
0. month	464.5±752.1	715.1±1017.6	–	NS	–	–
1. month	231.1±429.7	388.6±642.9	14.0±6.9	NS	0.001	0.001
3. month	81.8±83.1	494.9±403.4	229.1±171.3	0.003	NS	NS
6. month	30.4±40.0	973.7±858.5	820.4±535.5	0.001	0.001	NS
8. a month	5.0±0.0	1646.0±721.8	1295.7±732.8	0.001	0.001	NS

NS: statistically insignificant.

natal 0.1, 3, 6 and 8 months to monitor the natural course of anti-HBs antibodies transmitted from mother to baby by transplacental route. In 40.9%, 50%, 59.09% and 100% of infants anti-HBs titers fell below <10 mIU/mL at 1, 3, 6 and 8 months, respectively. Accordingly, anti-HBs antibodies that passed from mother to child completely disappeared in the 8th month, and these babies become anti-HBs-negative. Anti-HBs titers dropped below 10 mIU/mL in 40.9% of infants within a short period of one month and in all infants in the 8th month suggested that these children should be vaccinated early with HBV vaccine. However, in Group 2, anti-HBs titers of 20.83% of babies at 1 month were below 10 mIU/mL. This rate was 40.9% for unvaccinated babies in Group 1, which demonstrated that anti-HBs antibodies transmitted by transplacental route in 1st month did not affect the antibody response due to the HBV vaccine administered. In the third month, anti-HBs titers of 50% of the babies that make up Group 1 fell below 10 mIU/mL, all of the babies in Group 2 had anti-HBs titers above 10 mIU/mL. As is understood, it was observed that the anti-HBs titers of the vaccinated babies (Group 2) increased despite passive transmission of antibodies to the baby by transplacental route.

In the sixth month, while anti-HBs titers of 59.09% of babies in Group 1 fell below 10 mIU/mL, anti-HBs titers of all babies forming Group 2 were detected to be above 10 mIU/mL. In this case, anti-HBs antibody titers, which were passed passively through transplacental route, did not affect the antibody response due to HBV vaccine administered at 6 months. Finally, in the 8th month, all babies in Group 1 had anti-HBs – negative titers, while in all babies in Groups 2 and 3, anti-HBs titers were above 10 mIU/mL.

In conclusion, in this study, in accordance with the literature, it was detected that 99.8% of anti-HBs antibodies in the serums of mothers either naturally immune or via vaccination against HBV, transplacentally and passively passed to their babies. It was observed that anti-HBs antibodies passed passively through this transplacental pathway to the newborns decreased rapidly, and 100% of them became Anti-HBs-negative in the 8th month. The antibody response to the HBV vaccine administered to infants with these passively transmitted antibodies was found to be similar to the antibody response in infants whose mothers were vaccinated with the same vaccine schedule. Thus,

it was determined that anti-HBs antibodies that passed through transplacental pathway did not affect the antibody response that arose from the HBV vaccine administered at 0, 1 and 6 months.

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