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ORIGINAL ARTICLE

Comparison of immune response to hepatitis B vaccine between term and preterm infants at birth

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ABSTRACT

Background: Hepatitis B vaccination of the newborn prevents prenatal transmission of hepatitis B virus. American Academy of Pediatrics (AAP) recommends that preterm infants weighing less than 2000 grams at birth who born to HBS-Ag negative mothers should receive their first dose of hepatitis B vaccine as early as one month of age. The aim of the present study was to assess and compare the immune response of preterm and term infants to hepatitis B vaccine.

Materials and methods: Forty-eight preterm and 49 term neonates were enrolled for this case-control study. The vaccine was administered at birth, 1.5 and 9 months of age. Antibodies against hepatitis B surface antigen (Anti–HBS) were measured in all infants at 15 months of age.

Results: The study population included 24 boys and 24 girls with the mean birth weight of 1595.7±388.3 g. The mean gestational age of preterm infants was 32.4±2.1 weeks. Immune response to HB vaccine was protective and similar in both preterm and term infants (85.4 vs. 85.7%, NS). There was no significant association between the type of response and the infant's birth weight or sex. However, there were significant associations between antibody titer and use of mechanical ventilation and sepsis ($p<0.01$ for both).

Conclusion: Preterm and term infants have similar and effective response to hepatitis B vaccine when given immediately after birth.

Keywords: *Hepatitis B vaccine, Preterm infants, Immune response.*

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INTRODUCTION

Hepatitis B is a vaccine-preventable disease. In Iran, the rate of carriers is estimated to be 2.5-7.2 % (1). The risk of transmission from mother to child is about 40-50% that could be prevented by vaccination (2). The relationship between hepatitis B vaccine and prematurity was first described by Chawareewong (3). In 1992, American Academy of Pediatrics (AAP) recommended that all infants have to be immunized with hepatitis B vaccine before discharge (4). Since some studies showed that the level of antibody in preterm infants is lower than in term infants, AAP modified its recommendation in 1994 (5). Their new recommendation suggested that the first dose of hepatitis B vaccine should be delayed in infants

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less than 2000 g who born to HBsAg-negative mothers until they reach 2000 g of weight, two months of age, or the time of discharge (5). Although some studies showed the lower seroconversion in preterm infants than in term infants, controversies still exist because the differences in vaccine response were not significant and screening all mothers for HBsAg in different countries such as Iran is not possible. Some studies suggest the routine vaccine protocol for preterm infants immediately after birth (6), whereas others prefer the first dose of vaccine to be administered before discharge (7), and finally the last group recommends the routine vaccination followed by measuring antibody titers in 12-24 months and using additional dose of vaccine if necessary (8). In 1999, AAP in collaboration with Public Health Services published a guideline. They recommended that hepatitis B vaccination of term infants born to HBsAg-negative mothers should be delayed until 2 to 6 months of age (9). For premature infants, they suggested a delay in vaccination until infants reach a corresponding size and developmental level (9). However, the 2003 guideline of AAP recommends that the immunization of premature infants with birth weight less than 2000 g who born to HBsAg-negative mothers should be done as early as 1 month of age (10). In Iran, hepatitis B vaccination protocol for term and preterm infants is the same and to our knowledge, no study has been conducted to compare the responses of two groups to the vaccine. The main goal of the present study was to compare the immune response to hepatitis B vaccine in preterm and term infants.

PATIENTS and METHODS

A case-control study was performed on 48 term and 49 preterm infants during 2002-2003. They received hepatitis B vaccine at 0, 1.5, and 9 months of age according to the routine national vaccination protocol. 0.5cc (10µg) of a recombinant Cuban vaccine (Heberbiovac) was injected in gluteal muscle each time. Then, all infants were requested to attend Aliasghar and Akbarabadi hospitals at the age of 15 months. An informed consent was requested from their parents. Initial data including gestational age, sex, birth weight, HBs antibody titer, history of sepsis, use of mechanical ventilation and hospital admission were gathered. Then, in order to evaluate the HBs antibody titer, a 2cc-blood sample was taken and stored at -30°C until assayed in the laboratory of Iranian Blood Transfusion Organization (IBTO). For all samples, hepatitis B surface antibody (anti-HBs) was assayed using enzyme-linked immunosorbent assay (ELISA) method (Bio-Red kit). Antibody titers lower than 10 IU/ml were considered as negative response, between 10-100 IU/ml as a protective but poor response, and titers more than 100 IU/ml as an excellent response. All data were analyzed using SPSS software. Chi square and Student's t-test were used, when appropriate. A p-value of 0.05 or less was considered as significant.

RESULTS

Of the total 97 infants, 48 were preterm (case group) and 49 were term (control group). There were 24 and 26 boys in the case and control group, respectively. The mean birth weight was 1595.7±388.3 g. in the case and 3238.8±511.9 g in the control group. Mean gestational age of cases was 32.37±2.05 weeks, ranging 28-36 weeks. Positive response to vaccine was documented in 85.4% of cases, 85.7% of control subjects and 85.6% totally; however, the difference between groups did not reach a statistically significant level (Table 1). Furthermore, sex, gestational age, and birth weight failed to show associations with immune response (Table 2). Neither of the term infants had history of sepsis nor required mechanical ventilation. On the other hand, as presented in Table 3, there was a significant correlation between the immune response to hepatitis B vaccine and the history of sepsis and

necessity of mechanical ventilation among preterm infants ($p<0.01$).

Table 1. *Distribution of immune response to hepatitis B vaccine in term (control) and preterm (case) infants*

Immune Response	Case	Control	Total
Negative	7(14.6)	7(14.3)	14(14.4)
Poor	7(14.6)	8(16.3)	15(15.5)
Excellent	34(70.8)	34(69.4)	68(70.1)
Positive (poor+excellent)	41(85.4)	42(85.7)	83(85.6)
Total	**48(100)**	**49(100)**	**97(100)**

Table 2. *Distribution of immune response to hepatitis B vaccine according to the sex*

Immune Response	Girls	Boys	Total
Negative	8(17)	6(12)	14(14.4)
Poor	6(12.8)	9(18)	15(15.5)
Excellent	33(70.2)	35(70)	68(70.1)
Positive (poor+excellent)	39(83)	44(88)	83(85.6)
Total	**47(100)**	**50(100)**	**97(100)**

Table 3. *Distribution of immune response to hepatitis B vaccine in neonates with and without sepsis and necessity for mechanical ventilation*

Immune Response	Need for ventilation		Total
	Yes	No	
Negative	7(30.4)	0	7(14.6)
Poor	2(8.7)	5(20)	7(14.6)
Excellent	14(60.9)	20(80)	34(70.8)
Positive (poor+excellent)	16(69.6)	25(100)	41(85.4)
Total	23(100)	25(100)	48(100)

DISCUSSION

Our results reveal that the immune response of preterm infants to hepatitis B vaccine is similar to that of term infants. According to our findings, when the first dose of HB vaccine is administered at birth, in both term and preterm infants, the response to HB vaccine would not differ after 3 doses. This study had a good sample size (97 infants) and approximately 30% of the case group were very low birth weight (<1500 g) with similar level of protection to others. Immune response of preterm infants was not related to birth weight and gestational age. Thus, additional dose of vaccine in a 15-month preterm infant might not be required unless the antibody titer is checked in older ages. This finding compiles with the results of Bhave et al. that showed no difference between preterm and term infants in response to HB vaccine, and no benefit of vaccination deferment (6). Blondheim et al. showed that premature infants are able to have an immune response similar to mature neonates and there is no need to delay the vaccination (11). These findings were also confirmed by others, such as Del Canho et al. in Netherlands (12). They showed an antibody titer higher than 10 IU/ml in 95% of premature and mature infants who were vaccinated immediately after birth. In 1999, AAP recommended a delay of hepatitis B vaccination in premature infants until they reach 2000 g of weight or 2 months of age. This guideline was based on the research that showed among 99 preterm infants weighed <1750 g at birth, a high rate of seroconversion (79%) was observed in infants weighed <2000 g at the time of first immunization. Among preterm infants weighed over 2000 g and term infants, seroconversion was 91% and 100%, respectively (9). In 2003, AAP suggested a one-month deferment of HB vaccination in preterm infants <2000 g. Our data suggest that preterm infants are capable of developing an adequate immune response (85.4%) to hepatitis B vaccine. Khalak et al. in the United States, found 75% immune response in preterm infants and 71% in term infants (8). Kim et al. showed 90% immune response and Blonheim et al. found 93.5% positive response in term and 88.7% in preterm infants (11).Therefore, the rate of seroconversion in our population was in agreement with other studies and

small differences could be explained, in part, by ethnic and genetic variations (13). Although some studies have reported a relationship between birth weight and immune response, it can not be confirmed by ours.

We may conclude that there is no need to delay HB vaccination in preterm infants in Iran. In the present study, infants with the history of sepsis who required mechanical ventilation had lower antibody levels; this has been confirmed by prior studies (11). The present study obviates future studies to conclude the need for an additional dose of vaccine in neonates with history of sepsis that may require mechanical ventilation. Moreover, future studies might find the rate of HBsAg carrier mothers and probable role of maternal immunity for the time of hepatitis B vaccination. Finally, it is recommended to investigate the immunogenicity of the vaccine beyond 15 months of age and the need for booster vaccine.

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