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A comparison of post vaccination hepatitis B surface antibody level on the large and appropriate for gestational age infants

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Purpose: The aim of this study was to compare the hepatitis B surface antibody (HBs Ab) titer 1 month after the 4th dose of hepatitis B vaccine administration on the large and appropriate for gestational age infants.

Materials and Methods: This cross-sectional study was conducted on 7-month-old cases (n=132) divided into two groups of 2–4 kg (group 1: appropriate for gestational age, 63 cases) and >4 kg (group 2: large for gestational age, 69 cases), whom were vaccinated with a four-dose schedule of hepatitis B vaccine in 2016, Tehran, Iran.

Results: Mean birth weight of the groups was 2.98±0.528 and 4.19±0.190 kg, respectively. Hepatitis B surface antigen and hepatitis B core antibody were negative in all cases. HBs Ab level in group 1 and 2 was 13,701.00±11,744.439 and 8,997.15±2,827.191, respectively (95% confidence interval of difference, -7,607.44 to -1,800.25). There was a significant difference between the two groups in antibody titration and antibody logarithm level (p=0.002, p=0.0001).

Conclusion: Birth weight may affect the response to the hepatitis B virus vaccine administration.

Keywords: Birth weight, Hepatitis B surface antibody, Hepatitis B, Hepatitis B virus, Hepatitis B vaccines, Large for gestational age, Vaccines

Introduction

Hepatitis B is potentially a life-threatening liver infection caused by the hepatitis B virus (HBV). Chronic infection with HBV can progress leading to the development of hepatic cirrhosis and hepatocellular carcinoma [1,2].

The present prevalence of hepatitis B in Iran is 2.2% [1] and currently, about 1.4 million cases are infected with HBV all around our country. From this point of view, Iran is currently classified within the areas with a lower-intermediate prevalence [3]. According to the Iranian studies, over 50% of the mothers of hepatitis B surface antigen (HBs Ag) positive cases were also carriers [4,5]. It means that the route of perinatal transmission is the most likely route of transmission of HBV in Iran if the mother is HBs Ag positive and the neonate is not vaccinated at the right time. Perinatal transmission can occur at 3 different times: in-utero, during delivery, or after birth. Infection probably occurs predominantly at or after birth [5] and hepatitis B vaccination starting at birth is one of the most important ways to prevent this disease.

In addition, the rate of progression from acute to chronic HBV infection in perinatally acquired infection (90%) is more than infections between the age of 1 and 5 years

(20% to 50%) and adult acquired infection (<5%) [6]. Therefore, successful hepatitis B vaccination at birth could eventually decrease the chronic HBV infection.

From 1992, genetically engineered (or DNA recombinant) vaccine has been included in the expanded program of immunization (EPI) of Iran. At present, about 90% of Iranian infants are vaccinated against hepatitis B starting from birth and finishing by 6 months of age.

Since vaccination of neonates born to HBV positive mothers has a high success rate to prevent transmission of HBV, it is very important to minimize the risk of not responding to hepatitis B vaccination [5].

The induced Ab level after hepatitis B vaccination depends on the age at the time of immunization so that in comparison with infancy, after the age of 40 and by 60, the protective Ab level will drop from 95% to 90% and 65% to 75% of the cases respectively [7].

There are some studies revealing that the response to hepatitis B vaccine may also be affected by birth weight and the length of the needle used for vaccination [8,9] and preterm infants may have lower hepatitis B surface antibody (HBs Ab) titer after hepatitis B vaccination compared with full terms [7]. Obesity, the wrong site of vaccine administration, the fact of being small for gestational age and genetic determinants are factors that may decrease the host response to hepatitis B vaccine administration [10-13].

The current studies reveal that some immunosuppressive conditions such as chronic liver disease, chronic renal failure, diabetes mellitus, and advanced human immunodeficiency virus infection may reduce the response to this vaccine [7].

There are some concerns about the influence of birth weight on the level of HBs Ab in response to hepatitis B vaccination; in addition, the number of hepatitis B vaccine doses administrated in EPI of Iran is more than several other schedules; therefore, we conducted a study with the aim of comparing the HBs Ab titer 1 month after the completion of four doses of hepatitis B vaccine on the large and appropriate for gestational age infants.

Materials and Methods

This cross-sectional study was conducted on 7-month-old cases (n=132), who were born in Akbar Abadi Hospital, Tehran, Iran in 2016 and vaccinated with a full series of hepatitis B vaccine according to the EPI of Iran.

This research was performed after receiving approval from the ethics review committee of Iran University of Medical Sciences (IRB approval no., IR. IUMS.REC1394.26265). Informed consent was taken from the patient guardians before enrollment.

The height and birth weight of neonates were recorded by an experienced nurse immediately after birth and measured by the same means and scales for all cases.

Recombinant hepatitis B vaccine (0.5 mL, 10 μg; Pasteur Institute of Iran, IRC1228070570) stored at 2°C–8°C was administered to the cases using 23G disposable needles with 2.54 cm in length during the first day after birth. The injection was given in a standard way at 90° angle to the anterolateral thigh in the quadriceps muscle in accordance with the instructions of the Ministry of Health of Iran.

All cases received three doses of recombinant DNA hepatitis B vaccine as part of pentavalent vaccine provided by Biological E. Limited (Hyderabad, India) containing 12.5 μg HBs Ag in 0.5 mL at the ages of 2, 4, and 6 months according to the last (2014) national immunization program of Iran [14].

The infants were divided in two groups based on the birth weight (group 1: 2–4 kg, appropriate for gestational age; group 2: >4 kg, large for gestational age). The cases were recalled 1 month after receiving the last (fourth) dose of the hepatitis B vaccine at 7-month-old age to be enrolled again in the study. The exclusion criteria were maternal history of HBs Ag positivity, active hepatitis B infection, prematurity, birth weight less than 2 kg, blood exchange during the neonatal period, receiving intravenous immunoglobulin, hepatitis B immunoglobulin, blood, fresh frozen plasma, or any other blood products, documented congenital or acquired immunodeficiency.

Demographic and baseline data including birth details (birth weight, gestational age, any associated disease, and hospitalization) and anthropometric measures such as weight and height of the mother and infant at 7-month-old age were taken and recorded by the same observer using standard methods.

Hospital charts and official child health (the immunization records) were kept by parents and the dates of each vaccine administration were checked case by case by a pediatric resident.

At 7 months of age, 3 mL of venous blood were drawn (1 month after the fourth dose of hepatitis B vaccine administration) in both groups. Blood samples were centrifuged on the same day and the sera was collected and stored at −70°C for further testing. After about 60 to 90 days when all the samples were gathered, anti-HBs Ab was determined by Electrochemiluminescence (COBAS, Mannheim, Germany) following the manufacturer's instructions and expressed in international units/L (IU/L). An adequate antibody response was

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defined as HBs antibody titer ≥10 IU/L.

Initially, the parametric status and distribution of data were checked by two-sample Kolmogorov-Smirnov test. All statistical analyses were performed using Stata ver. 12.0 (Stata Corp., College Station, TX, USA). Quantitative data were expressed as mean±standard deviation (SD) and qualitative data were reported as percentage. Means were compared using T-test, and, chi-square test was used for categorical variables. The level of significance was considered <0.05.

Results

In this study, 132 infants aged 7 months based on birth weight were evaluated and divided in two groups: 2–4 kg (63 cases, 47.72%) and >4 kg (69 cases, 52.27%). Mean birth weights (±SD) in two groups were 2.98±0.528 and 4.19±0.190 kg, respectively. Descriptive and analytic variables of these two groups are compared and shown in Table 1. HBs Ag and hepatitis B antibody to core antigen were negative in all cases.

In this study, the mean log of Ab titers was reported in order to normalize these means more. The mean log (HBs antibody titer) for groups 1 and 2 were 3.60±0.232 and 3.79±0.302

Table 1. Comparison of characteristics between the two groups with birth weight of 2–4 kg and >4 kg

Characteristic	Group 1	Group 2	p-value	95% CI of difference
Quantitative variables				
Apgar score (up to 10)	8.92±0.326	8.94±0.291	0.691	-0.128 to 0.085
Gestational age (wk)	38.06±2.24	39.05±1.67	0.004*	-1.6716 to -0.3173
Birth-height (cm)	49.46±3.27	53.29±3.17	0.0001*	-4.9406 to -2.7184
7-Month height (cm)	67.18±4.78	70.67±2.86	0.0001*	-5.1379 to -1.8456
7-Month weight (kg)	7.98±1.12	8.67±1.15	0.001*	-1.0724 to -0.3061
Birth-BMI	12.5±1.55	14.93±2.32	0.0001*	-3.4694 to -2.0930
7-Month BMI	18.21±4.94	17.45±1.95	0.321	-0.7537 to 2.2719
Mother's weight (kg)	70.94±15.85	73.78±13.20	0.282	-8.0212 to 2.3554
Mother's height (m)	1.61±0.06	1.61±0.06	0.469	-0.0318 to 0.0148
Mother's BMI	27.31±5.87	28.13±4.76	0.396	-2.7177 to 1.0834
Qualitative variables				
Gender (male)	35 (56.6)	43 (62.3)	0.430	
Delivery (NVD)	32 (50.8)	28 (40.6)	0.239	
Nationality (Iran)	53 (84.1)	50 (72.5)	0.170	
Birth Icterus (yes)	14 (22.2)	10 (14.5)	0.250	

Values are presented as mean±standard deviation or number (%). Group 1: birth weight 2–4 kg; group 2: birth weight >4 kg.
CI, confidence interval; BMI, body mass index; NVD, normal vaginal delivery.
*Significant difference.

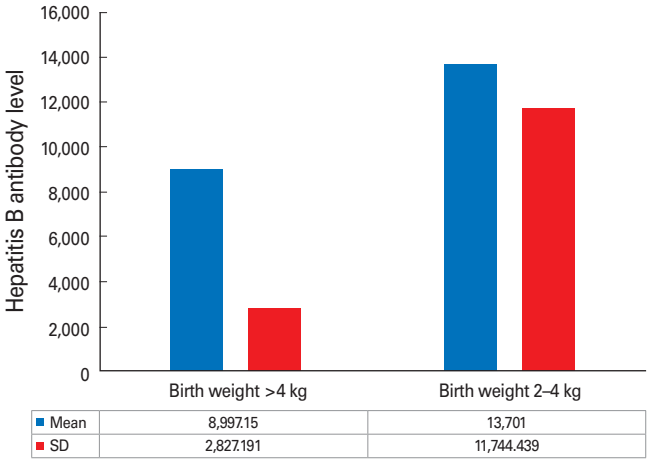

Fig. 1. Comparison of hepatitis B antibody level (titer) between the two groups with birth weight of 2–4 kg (right) and >4 kg (left) (p-value=0.002). SD, standard deviation.

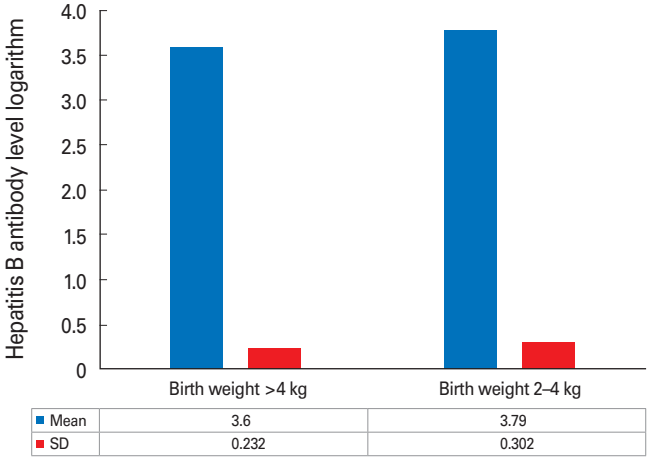

Fig. 2. Comparison of hepatitis B antibody level (log) between the two groups with birth weight of 2–4 kg (right) and >4 kg (left) (p-value=0.0001). SD, standard deviation.

Table 2. Comparison of anti-hepatitis B antibody level between the two groups

Variable	Group 1 (birth weight: 2–4 kg) (n=63)	Group 2 (birth weight >4 kg) (n=69)	Mean difference	p-value	95% CI of difference
Hepatitis B antibody level	13,701.00±11,744.439	8,997.15±2,827.191	4,703.84±1,518.754	0.002	-7,607.44 to -1,800.25
Log antibody	3.79±0.302	3.60±0.232	0.18±0.046	0.0001	-0.279 to -0.094

Values are presented as mean±standard deviation.

(95% confidence interval for difference, -0.279 to -0.094), respectively. As shown in Figs. 1 and 2 and Table 2, there were significant differences between the two groups in antibody titration level and antibody level logarithm (p=0.002 and p=0.0001), respectively.

Discussion

Hepatitis B is still one of the major health problems in Iran and worldwide. Fortunately, this infectious disease is preventable and hepatitis B vaccine administration is one of the most important ways to prevent it. According to the EPI of Iran, hepatitis B vaccination is recommended for all neonates soon after birth and before hospital discharge. The current vaccine is 95% effective in prevention of HBV infection [15].

Usually, the primary vaccination in children consists of three intramuscular doses of vaccine and the usual schedule is vaccination at 0, 1 to 2, and 6 to 18 months of age. From 2014, the EPI of Iran has included a pentavalent (consisting hepatitis B, diphtheria, tetanus, pertussis, and hemophilus influenza) vaccine administered at 2, 4, and, 6 months of age. Since the first dose of hepatitis B vaccine is administered at birth, currently the total received doses of this vaccine is four doses which contain one dose more than the most other used international schedules.

In our study, a difference was found in the mean HBs antibody titer in the two groups of 2–4 kg and >4 kg birth weight when evaluation was performed 1 month after the completion of primary hepatitis B vaccination schedule. Ozdemir et al. [9] evaluated the influence of the length of the needle on the HBs Ab level in 7-month-old infants with >4 kg birth weight and revealed a significant difference of HBs Ab level when the needle with a standard length was used in comparison to a needle with 2.54 cm of length. The length of the needle used in health centers of Iran for neonates and infants is 25 mm for any weight. However, we found a significant difference in the two groups in terms of HBs Ab level. So, it seems that the length of the needle might not be the main cause of this difference. The result of our study is in concordance to the result of Çekmez et al. [8]. They revealed that infants with the birth weight of >4 kg had a lower response to hepatitis B vaccine in comparison to normal and small for gestational age cases. However, we can claim that with Iran's current schedule, there is no concern about the birth weight and the length of syringe used because the Ab level was in a protective range in both groups despite a significant difference.

Since the assessment of the HBs Ab level was performed at the age of 7 months in this study, we could rather rule out the effect of previous maternal immunization before or during pregnancy. In fact, we did not have the HBs Ab level of the mothers during the pregnancy but since the sampling of the infants was after 6 months, the effect of Ab level of the mothers on the Ab level of the infants could be inconsiderable.

Regardless of birth weight, the results of this study revealed a very good response to the hepatitis B vaccine as a part of pentavalent vaccine in the evaluated population. In addition, it seems that unlike preterm and small for gestational age neonates, weight-based policy for hepatitis B vaccination is not necessary for "large for gestational age" neonates in Iran. Of course, it should be noted that the current Iranian protocol recommends four doses of hepatitis B vaccine for all infants regardless of birth weight. It is recommended to repeat this study in the countries with three-dose schedule of hepatitis B vaccine to evaluate whether the same results will be achieved with their program.

An important point, however, could be the number of vaccine doses used in EPI of Iran. Although there are some concerns about the down regulation of immune system in response to several doses of hepatitis B vaccine, the results of this study reveals that the administration of fourth dose, at least in short time, does not interfere with the Ab level production.

Our study had some limitations. We did not have access to the cord blood of the cases so we were confined to the HBs Ag status of the mothers which was checked during the health care program visits of the pregnant women. Our sample size was small so it is recommended to repeat this study in a larger population.

In conclusion, the results of this study might have an important public health implication that the level of HBs Ab in response to hepatitis B vaccination in 7-month-old infants with birth weight of >4 kg is still in the protective level. However, the trend of HBs Ab level of cases with birth weight of >4 kg has not yet been studied in older age in Iran. Therefore, it is suggested to design a similar study for children and adolescents to compare the HBs Ab level of the two groups with birth weight of 2–4 kg and >4 kg in older age.

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