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Does Blood Type Have an Effect on Response to Hepatitis B Vaccine in Children? Single Center Data

Kan Grubunun Çocuklarda Hepatit B Aşısına Yanıt Üzerinde Etkisi Var mı? Tek Merkez Verileri

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Abstract

Objective: Hepatitis B virus infection still remains a global health issue. Many factors may affect immune response to hepatitis B vaccination, and in this regard, we aimed to investigate the possible relation between blood types and hepatitis B vaccine response.

Material and Methods: In this study, the data of 282 cases in the patient group and 299 cases in the control group, aged between 1-18 years, who were administered three doses of recombinant hepatitis B vaccine between January 2016 and June 2018, were compared. Hepatitis B antibody status and blood types were retrospectively obtained. Anti-HBs status and blood type were investigated.

Results: Blood group of A was the most frequently detected type at a number of 247 (42.5%). The average age of the children was 9.60 ± 4.44 in the hepatitis B surface antibody (anti-HBs) negative group and 9.64 ± 5.02 in the anti-HBs positive group. There was no statistically significant difference in age comparison between anti-HBs positive and negative children. In the evaluation performed to evaluate the correlations between age and anti-HBs titer in the anti-HBs positive group, no significant correlation was found between age and titer. Multivariate analyses of blood type, sex and age demonstrated that having group A blood type were found to be associated with negative anti-HBs.

Conclusion: Our results showed having A blood type could be a negative risk factor in terms of creating a sufficient immune response to hepatitis B vaccination.

Keywords: Immunity, children, hepatitis B vaccination, blood type

Öz

Giriş: Hepatit B virüsü enfeksiyonu halen küresel bir sağlık sorunu olmaya devam etmektedir. Hepatit B aşısına karşı immün yanıtı birçok faktör etkileyebilir, bu bağlamda çocuklarda kan grupları ile hepatit B aşısına yanıt arasındaki olası ilişkiyi araştırmayı amaçladık.

Gereç ve Yöntemler: Bu çalışmada Ocak 2016 ile Haziran 2018 tarihleri arasında 1-18 yaş arası, üç doz rekombinant hepatit B aşısı uygulanan, hasta grubundan 282 ve kontrol grubundan 299 olgunun verileri karşılaştırıldı. Hepatit B antikor durumu ve kan grupları geriye dönük olarak elde edildi. Anti-HBs durumu, kan grubu ve bu parametrelerin ilişkisi araştırıldı.

Bulgular: A kan grubu 247 (%42.5) hasta ile en sık tespit edilen kan grubu oldu. Hepatit B yüzey antikoru (anti-HBs) negatif grupta çocukların yaş ortalaması 9.60 ± 4.44, anti-HBs pozitif grupta ise 9.64 ± 5.02 idi. Anti-HBs pozitif ve negatif çocuklar arasında yaş karşılaştırmasında istatistiksel olarak anlamlı bir fark yoktu. Anti-HBs pozitif grupta yaş ile anti-HBs titresi arasındaki korelasyonları değerlendirmek amacıyla yapılan değerlendirmede yaş ile titre arasında anlamlı bir ilişki bulunamadı. Kan grubu, cinsiyet ve yaşa ilişkin çok değişkenli analizler, A grubu kan grubuna sahip olmanın negatif anti-HBs ile ilişkili olduğunu gösterdi.

Sonuç: Sonuçlarımız, A kan grubuna sahip olmanın, hepatit B aşısına yeterli bağışıklık tepkisi oluşturma açısından olumsuz bir risk faktörü olabileceğini gösterdi.

Anahtar Kelimeler: Bağışıklık, çocuklar, hepatit B aşısı, kan grubu

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Introduction

ABO and Rh blood group classification systems are the most widely used classification systems based on the presence of genetic antigens on the surface of red blood cells (1). It has been shown in many studies that antibodies and antigens are hereditary characteristics and that differences in blood group expressions affect the susceptibility of individuals to infections and chronic diseases (2-5). The relationship between blood group antigens and diseases has not been fully elucidated, but studies have shown that these antigens can serve as receptors or ligands for microorganisms (6,7).

The human ABO blood group system is the only system that displays antibodies produced complementary to the ABO blood group, called isoantibodies (anti-A in individuals B, anti-B in individuals A, anti-A and anti-B in individuals O, and none in individuals AB). Levels of isoantibodies vary significantly between individuals and determine an individual's general predisposition to form antibodies against antigens. Therefore, it is an indicator of the individual's functional immunological capacity and can be used to predict immune response to the vaccine (8,9). The levels of some interleukins are different in individuals with different blood groups. This situation is associated with differences in antibody responses and increased risk against some diseases (10,11). In addition, blood groups can also affect the formation of memory T cell responses, which are very important in vaccine response (12).

The vaccination of individuals is the most effective approach in terms of preventing hepatitis B virus (HBV) infection (13,14). Many factors may affect the immune response to hepatitis B vaccination (14-16). It is accepted as protective when hepatitis B surface antibody (anti-HBs) titer reach≥ 10 mIU/mL (17-19).

In recent years, more and more attention has been paid to the relationship between ABO blood types and many human diseases, and there has been evidence that ABO blood types may be associated with infection, cardiovascular disease, and malignant tumorigenesis (20-22). In addition, possible relationships between the immune system and blood types have led people to investigate the relationship between the antibody response to vaccines and blood types. When the literature was examined, it was seen that the relationship between rotavirus vaccines, cholera vaccine, rabies vaccine, SARS-CoV-2 vaccine and blood groups was investigated, but the relationship between HBV vaccine and blood groups was not investigated (8,12,23-26).

Our aim in this study was to investigate the effect of blood groups on the anti-HBs response after hepatitis B vaccine administration.

Materials and Methods

Study population

A total of 2.138 pediatric patients aged 1-18 years, who applied to the pediatric outpatient clinic of Gaziantep University Hospital between January 2016 and June 2018, for any reason, were included in this study. The laboratory results of the cases, disease status, age, sex, nutritional status, and vaccination history were obtained retrospectively from hospital records based on national vaccination cards. Afterwards, the vaccination history of the subjects included in the study was confirmed by calling their families by phone.

The patient group included 282 patients who were found to be anti-HBs negative as a result of retrospective evaluation. All patients in the patient group received three doses of the hepatitis B recombinant vaccine, which is included in the national immunization program, in the first year of life, and at least one month had passed since the last vaccine dose. One thousand eight hundred and fifty-six cases were excluded from the study. Exclusion criteria were as follows: Failure to obtain anti-HBs antibody result, positive anti-HBs test result, hepatitis B surface antigen (HBsAg) positive, failure to receive three doses of hepatitis B recombinant vaccine within the first year of life, smoking, use of immunosuppressive drugs, use of corticosteroids, and having any chronic disease (e.g. obesity, protein energy deficiency, malignancy, autoimmune disease, rheumatological disease, immune system disorder, chronic hepatitis B).

Data collection consisted of three steps to minimize bias. In the first stage, the records of all children who applied to the pediatric outpatient clinics between the above-mentioned dates, had a history of vaccination and were able to access their records were obtained. Birth dates and sexes of these children were also recorded. In the second stage, among the cases selected at the first stage, all children who were tested for anti-HBs antibodies and were found to be negative were recorded as antibody-negative group without blood group information. The first two stages were carried out without the knowledge of the children's blood groups. In the third stage, among the children selected in the first two stages, those whose blood group information could be accessed from the hospital records were recorded. All cases registered at the end of these three stages were questioned again in terms of exclusion criteria, and a total of 282 cases were included in the study in the patient group and statistical analysis was performed.

The selection of the control group was made by the same method mentioned above. Unlike the patient group, the cases with positive anti-HBs in the second stage were recorded. At the end of all stages, since we wanted to have approximately

the same number of control groups as the patient group, the number of cases in the control group was terminated by recording the information of the first 299 cases.

Labarotory analyses

HBsAg and anti-HBs titers were measured with ARCHITECT anti-HBs and HBsAg assays and titers for anti-HBs over 10 mIU/mL were accepted seropositive. The detection of blood types was made with Abbott 1200 kits Ortho machine and they were classified as A, B, O and AB. The associations of hepatitis B vaccine response with blood type, sex and age were evaluated.

Ethics

Ethics approval for the conduct of the study was obtained from the Institutional Review Board (Approval no:2018/280).

Statistical Analysis

Statistical analyses were made with Statistical Package for the Social Sciences (SPSS) 20 statistical software. Categorical variables were presented as number and percentage and compared using the Chi-square test. The Kolmogorov-Smirnov test was used to check whether data followed a normal distribution. In addition, multivariate analyses was performed for the age, sex and blood type effect on anti- HBs positivity variable using logistic regression. In addition, Spearman's rho (r) was calculated to assess the correlation between continuous data. Statistical significance level was set at $p< 0.05$.

Results

A total of 282 cases, 51% (144) boys and 49% (138) girls, with a mean age of 9.60 ± 4.44 years in the patient group, and 54% (162) boys and 46% (137) girls, a total of 299 cases with a mean age of 9.64 ± 5.02 years in the control group, were included in our study. No statistically significant difference was found between the patient and control groups in terms of age and sex ($p= 0.94$, $p= 0.45$).

Among the patients included in the study, 143 (50.7%) patients were from the A blood group, 50 (17.8%) from the B blood group, 21 (7.4%) from the AB blood group, and 68 (24.1%) from the O blood group. And in the control group, 104 (34.9%) patients were from A blood group, 66 (22.0%) from B blood group, 26 (8.7%) from AB blood group, and 103 (34.5%) patients from O blood group. Among all the cases included in the study, A blood group was the most common with 247 (42.5%) cases and AB blood group was the least detected with 47 (8.08%) cases (Table 1).

In the statistical evaluation performed to evaluate the correlations between age and anti-HBs titer in the anti-HBs positive group, no significant correlation was found between age and titer ($r= -0.18$, $p= 0.753$).

Blood group, sex and age multivariate analyzes showed that having group A blood group was associated with negative anti-HBs (Table 2). In the statistical evaluation made between age and blood group type in anti-HBs negative and positive groups, no statistically significant difference was found between the groups (Table 3).

Discussion

Hepatitis B virus infection (HBV) still remains a global health issue. HepB vaccine is the basis of HBV prevention efforts. Administration of the first dose of hepatitis B vaccine within the first 24 hours of life and later on additional two doses is 90-95% effective in terms of preventing HBV infection. The titer of anti-HBs≥ 10 mIU/mL is called as seroprotection and accepted protective against HBV infection (18,19). Individuals with

Table 1. Distribution of anti-HBs status among different blood group types

	Anti-HBs Status		
Blood Group Type	**Negative (n, %)**	**Positive (n, %)**	**Total (n)**
A	143 (50.7)	104 (34.9)	247
B	50 (17.8)	66 (22)	116
AB	21 (7.4)	26 (8.7)	47
O	68 (24.1)	103 (34.5)	171
Total	282 (100)	299 (100)	581

Table 2. Multivariate analyses of age, gender and blood type on anti-HBs positivity

Variable	**B**	**Exp(B) (95%CI)**	**p**
Gender (Male)	0.169	1.185 (0.850-1.651)	0.317
Age	0.001	1.001 (0.967-1.036)	0.959
A Blood Group	- 0.743	0.476 (0.320-0.708)	<0.001
B Blood Group	- 0.130	0.878 (0.544-1.418)	0.596
AB Blood Group	- 0.205	0.815 (0.425-1.565)	0.539

Table 3. Age difference between anti-HBs positive and negative children

	Anti-HBs Status	Age	p
Group A	Positive (104)	9.44 ± 4.99	0.901
	Negative (143)	9.51 ± 4.47	
Group B	Positive (66)	9.92 ± 5.08	0.986
	Negative (50)	9.94 ± 4.39	
Group AB	Positive (26)	9.42 ± 4.75	0.868
	Negative (21)	9.19 ± 4.71	
Group O	Positive (103)	9.72 ± 5.15	0.928
	Negative (68)	9.66 ± 4.41	

normal immune system who had three doses of vaccination are presumed to develop lifelong immunity against HBV infection (27). Although universal vaccination could induce protective antibodies in most healthy children after a routine primary series of hepatitis B vaccines, the duration of protection after the primary series of vaccines remains unknown. Unfortunately, there is currently no consensus on the necessity of anti-HBs titer control after hepatitis B vaccination or booster vaccination (28).

Lee et al., in their study with 5.650 cases aged 0-18 years, have stated that the anti-HBs titer was negative in approximately 25% of the cases and anti-HBs titer decreased with the increase in age. They recommended checking the anti-HBs titer in children going to school, especially in the 13-14 age range, and administering booster vaccine if necessary (17). Kim et al. and Alssamei et al. have indicated that revaccination or booster doses should be considered for vaccinated children (29,30). Costa et al. have shown that patients with chronic kidney disease (CKD) had significant decreases in anti-HBs titers over time. They recommended that the anti-HBs titer should be checked before or during dialysis in children with CKD, and a repeat dose of vaccination should be given if it is found below the protective titer (31). Contrary to these studies, Hunter et al, in their work, have stated that the routine check of titer is not recommended except in people who are immunocompromised or healthcare workers (32).

In studies, the relation of ABO blood types with some diseases or typical laboratory findings have been demonstrated (1,20). Cserti et al. have shown in 2007 that individuals with blood type 0 are less likely to be infected with plasmodium malaria (32). This finding was also supported later on in the same year by experimental studies of Rowe et al (33). Harris et al. have shown that individuals with O blood group develop more severe infection with *Vibrio Cholerae O1 El tor* and *O139* strain (34).

Studies have shown that some interleukins are higher or lower in people with certain blood types, and this is associated with an increased or decreased risk of developing certain diseases (10,11). Gil-Manso et al. have stated in their study that blood groups may affect the formation of memory T cell responses. In addition, they have stated that the intensity of the humoral immune response and memory T cell response may be related to ABO blood group and age (12).

Immune response to vaccines requires activation of T lymphocytes by antigen-presenting cells, which then helps B lymphocytes transform into antibody-producing plasma cells. So, there is a T-lymphocyte dependent response (35). Various cytokines and interleukins such as interleukin 4, 5, 12 are required for the maturation of T lymphocytes to a Th1 or Th2 response and for B lymphocytes to differentiate into antibody-secreting plasma cells (36). The level of interleukins, which are effective in the immune response to vaccines, is different in individuals with different blood groups (37).

Factors associated with low immunological response to hepatitis B vaccine in various studies are as follows: "Being in the pediatric age group; being born prematurely or with a low birth weight; being a member of a family that is a carrier of hepatitis B; having a previous history of blood transfusions; being a liver transplant recipient; having an underlying malignant disease, liver disease, rheumatologic disease, or corticosteroid-resistant nephrotic syndrome; being on corticosteroid therapy; being a healthcare worker" (27,28,35).

The literature review revealed that studies on the relation between vaccination response and blood types are scarce, while many studies available are focused on the associations between blood types and infectious diseases or acute-chronic diseases. In 2005, Buchta et al. investigated the relationship between the immune response to rabies vaccination and ABO blood group and showed that there was no relationship between them (8). Studies between blood group antigens and rotavirus vaccine have indicated that blood types are unlikely to contribute to existing population differences in rotavirus vaccine efficacy between high- and low-income countries (23-25). Studies have reported that one of the genetic factors involved in explaining the variability in cholera susceptibility or immune response to a cholera vaccine is the ABO blood group system (26).

Based on all these suggestions and theories, in our study, we compared the blood groups of healthy children with anti-HBs negative and anti-HBs positive. Since we aimed to determine the relationship between blood types and anti-HBs negativity, an equal number of both anti-HBs positive and negative children were included in the study. Therefore, our numbers did not reflect the anti-HBs seroprotection rates in the population. As mentioned above, seroprotection is not expected to be 100%, and it is expected that the anti-HBs titer will decrease over time. Although this reduction does not seem to be significant for healthy individuals in terms of protection from infection, it may be significant for patients at risk and may make them vulnerable to infection. Our analyzes showed that children with blood group A had more anti-HBs negativity than other blood groups (57.9%). Furthermore, when we performed multivariate analysis for sex, age, and blood type, having A blood type was associated with being anti-HBs negative. It has been shown in many studies that seroprotection decreases over time in people vaccinated in infancy, and a booster vaccine dose is also recommended in some studies. However, this is still controversial (38-40). When we evaluated the relationship between age and anti-HBs titer in our study, no statistically significant correlation was found between age and titer in the anti-HBs positive group (r= -0.18, p= 0.753). Our multivariate regression analyzes showed that blood type may be important in the development of serological response to hepatitis B vaccine. Therefore, based on our findings, blood type A can be considered a risk factor for decreased seroprotectiveness. In the light of these findings, the necessity of regularly checking the antibody status of children with A blood group and administering a booster dose to these individuals can be discussed. This can be both an easier and less costly method to implement.

Conclusion

Considering the much higher cost of treatment than vaccination, it may be a more accurate approach to regularly check antibody titers against HBsAg and be vaccinated in high-risk individuals. Therefore, our results suggest that having blood type A may be an adverse risk factor for inducing an adequate immune response to vaccination.

Limitations

Our study was not planned prospectively.

Since our study was not planned prospectively, booster vaccination and its results after the patients found to be anti-Hbs negative were unfortunately not available and were not mentioned in the article. This is one of the important limitations of our study.

With prospective and large-scale studies to be carried out with a larger number of patients and control groups, the cases should be followed up from birth, and the relationship between anti-HBs negativity and age and blood groups should be determined.

Ethics Committe Approval: This study was obtained from Gaziantep University Clinical Research Ethics Committee (Decision no: 2018/280, Date: 10.10.2018).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - HU; Design - HU; Supervision - MEC; Resource - MEC, HU; Data Collection and/or Processing - MEC; Analysis and/or Interpretation - MEC, HU; Literature Search - HU; Writing - MEC, HU; Critical Review- MEC, HU.

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