Booster Dose Vaccine Response among Children Who were Primary Hepatitis B Vaccine Non-Responders and Sensitive Groups Concerning Vaccine Response

Birincil Hepatit B Aşı Yanıtsız Çocuklarda Hatırlatma Doz Aşı Yanıtları ve Aşı Yanıtında Hassas Gruplar

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ABSTRACT

Objective: In this study, booster dose vaccine response was evaluated after performing a vaccine schedule at 0, 1st and 6th months among 83 children aged between 2 and 16 years who were primary hepatitis B vaccine non-responders and we tried to determine which groups were sensitive concerning vaccine response.

Material and Methods: Euvax B vaccine which included 10 µg HBsAg was administered in 3 doses for the second time at 0, 1 and 6 months as 0.5 ml intramuscularly in the deltoid muscle to 83 healthy children aged between 2 and 16 years who were primary hepatitis B vaccine non-responders and their vaccine status was determined with tests before minor surgery. Blood tests were taken three times from children at 1, 6 and 7 months after the first vaccination and anti-HBs titer was evaluated by using enzyme-linked immunosorbent assay technique.

Results: The mean age of the children was 9.3±3.6 years (2-15,9 years). The anti-HBs geometric mean concentration was found to be 537.97±377.51 mIU/mL (0.6-1000) after the first vaccination, as 309.33± 337.45 mIU/mL (8-1000) after the second vaccination and as 609.78±347.43 mIU/mL (11.1-1000) following the third vaccination. Anti-HBs positive conversion rates in T1 were compared in 81 children who had been checked after the first vaccination and anti-HBs positive conversion rates were found to be significantly lower in children whose anti-HBs titer was under 1 mIU/ml before vaccination (p=0,01, Z -3.29, U 469). There was no difference concerning T6 and T7 between these two groups. Anti-HBs positive conversion rates in T6 and T7 were found to be significantly higher in children with malnutrition (p=0.008, Z -2.56, U 60.5, p=0.03, Z -2.11, U 26.5).

Conclusion: When observing the rapid decrease in T6 in contrast with the two dose vaccination, it is thought that anti-HBs seroconversion rates and anti-HBs geometric mean concentration are related with reminding, anti-HBs titer before vaccination and checking time of anti-HBs rather than the number of reminding doses. In fact, we believe that 3 dose vaccination is better among those children whose anti-HBs titer is under <1 mIU/mL and who have malnutrition.

Key Words: Booster vaccination, Child, Hepatitis B virus, Unresponsiveness

ÖZ

Amaç: Çalışmada birincil hepatit B aşı yanıtsız 2-16 yaş aralığındaki 83 çocukta, 0, 1 ve 6. ay aşı şeması uygulanarak elde edilen hatırlatma doz aşı yanıtları değerlendirilmiş ve aşı yanıtında hassas gruplar belirlenmeye çalışılmıştır.

Gereç ve Yöntemler: Küçük cerrahi girişimler öncesi yapılan tetkikler sonrasında birincil hepatit B aşı yanıtsızlığı saptanan 2-16 yaş aralığındaki sağlıklı 83 çocuğa, 2. kez 0, 1 ve 6. aylarda 3 doz 10 µg HBsAg içeren Euvax B aşısı deltoid kasa 0.5ml kas içine uygulanmıştır. Çocuklardan birinci aşıdan 1, 6 ve 7. ay sonra olmak üzere, 3 kez kan alınarak anti-HBs titresi enzyme-linked immunosorbent assay tekniği ile değerlendirilmiştir.

Bulgular: Çocukların yaş ortalaması 9.3±3.6 yıl (2-15.9) bulunmuştur. Birinci aşı sonrası anti-HBs ortalama geometrik konsantrasyonu 537.97±377.51 mIU/mL (0.6-1000), 2. aşı sonrası 309.33± 337.45 mIU/mL (8-1000), 3. aşı sonrası 609.78±347.43 mIU/mL (11.1-1000) bulunmuştur. Birinci aşı sonrası tetkik yapılabilen 81 çocuk arasında T1'de anti-HBs-positive serokonversiyon oranı, aşı öncesi anti-HBs titresi 1 mIU/mL'nin altında olan çocuklarda diğer gruba göre

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istatistiksel anlamlı biçimde daha düşük bulunmuştur (p=0.01, Z -3.29, U 469). Bu 2 grup arasında T6 ve T7'de istatistiksel fark saptanmamıştır. Malnütrisyonlu hastalarda T6 ve T7'de anti-HBs positive serokonversiyon oranı diğer gruba göre istatistiksel anlamlı olarak daha yüksek bulunmuştur (p=0.008, Z -2.56, U 60.5, p=0.03, Z -2.11, U 26.5).

Sonuç: İki doz aşıya rağmen T6'daki hızlı düşüşe bakıldığında, anti-HBs serokonversiyon oranı ve anti-HBs ortalama geometrik konsantrasyon değerleri hatırlatma doz sayısından ziyade, hatırlatma yapılmasına, aşı öncesi anti-HBs titresine ve anti-HBs titresi bakma zamanıyla ilgili gözükmektedir. Ancak, aşı öncesi anti-HBs titresi <1 mIU/mL olanlar ve malnütrisyonlu çocuklarda 3 doz aşılamanın daha doğru olacağı kanaatindeyiz.

Anahtar Sözcükler: Hatırlatma aşılaması, Çocuk, Hepatit B virüs, Cevapsızlık

INTRODUCTION

Viral hepatitis B is a public health problem and there are no specific drugs to treat hepatitis B virus (HBV) infection. For susceptible populations, the most effective preventive measure is to improve immune competence by immunizing with a hepatitis B vaccine (1). Several studies have found that unresponsiveness to the primary hepatitis B vaccination is seen in 1-15% of the cases (2,3).

In this study, booster dose vaccine response was evaluated after performing a vaccine schedule at 0, 1 and 6 months 83 children aged between 2 and 16 years who were non-responders to the primary hepatitis B vaccine. Moreover we tried to determine which groups were sensitive to vaccine response.

METHODS

The study was conducted between 1 August 2015 and 1 May 2016 at the University of Health Sciences, Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital. 83 children were included in the study. All of the children were informed of the completion of the first vaccine series of hepatitis B 3 doses. Hepatitis B surface (HBsAg) antigen, antibody to hepatitis B surface (anti-HBs) antigen, and antibody against hepatitis B core (anti-HBc) antigen titers were examined by enzyme-linked immunosorbent assay (ELISA) technique before any minor surgery. In children, HBsAg and anti-HBc were found (-), anti-HBs titer was found to be <10 mIU/mL and they were directed to the Well Child Unit for hepatitis B vaccination. Children with immune deficiency, chronic diseases or a history of hepatitis were excluded from the study.

Euvax B (Sanofi Pasteur Ltd., Thailand/LG Life Sciences Ltd., Korea [batch no. UVA14046]) vaccine which included 10 µg HBsAg was performed by the same nurse in 3 doses for the second time at 0, 1 and 6 months as 0.5 ml intramuscularly in the deltoid muscle to the children. The vaccines were used within the dates of validity. Blood tests were taken three times from the children at 1 (T1), 6 (T6) and 7 (T7) months after the first vaccination, and anti-HBs titer was checked by ELISA method. Anti-HBs titers of <10 mIU/mL were considered as negative; anti-HBs titers of ≥10 mIU/mL were considered as positive (4). 25.3% (21/83) of the children had been vaccinated with 2 doses and 62 (74.7%) children had been vaccinated with 3 doses. Anti-HBs titer was checked in 97.6% (81/83) of the children before the second vaccination (T1), in 74.7% (62/83) of the children before the third vaccination (T6) and 49.4% (41/83) of the children one month after the third vaccination (T7).

Ethical approval was obtained for this study from University of Health Sciences, Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital Ethical Committee.

Statistical analysis

The statistical software SPSS 17.0 was used for statistical analysis. Descriptive statistics were employed. Wilcoxon Signed Rank test was used for dependent groups and Mann-Whitney U test was used for independent groups. Differences were considered statistically significant with P values of <0.05.

RESULTS

There were 36 (43.3%) girls and 47 (56.7%) boys. Their mean age was 9.3±3.6 (2-15.9) years. According to body mass index percentile rates, 9 (10.8%) of the children had malnutrition, 14 (16.8%) of the children were obese and 60 (72.4%) showed normal weight. Forty seven (56.6%) of the children had been exposed to tobacco smoke. Family members or first degree relatives of twenty nine (34.9%) children were HBV carriers.

The mean duration after the primer vaccination schedule was found as 8.8±3.6 (1.5-15.4) years. Before the booster vaccination, the anti-HBs geometric mean concentrations (GMCs) of the children were found to be 2.37± 2.53 mIU/mL (0.0-9.45), and the anti-HBs titer was under < 1mIU/mL in 44.6% (37/83) of the children. A protective antibody titer was found in all 83 children whose anti-HBs titer was checked. Anti-HBs titer was found a as <10 mIU/mL among four children (4.9%) whose anti-HBs titer was checked before the second vaccination, three of these children had efficient anti-HBs titer after the second vaccination and one of these children had efficient titer after the third vaccination.

Anti-HBs GMCs was found as 537.97±377.51 mIU/mL (0.6-1000) in T1, 309.33± 337.45 mIU/mL (8-1000) in T6 and 609.78±347.43 mIU/mL (11.1-1000) in T7. A 227 fold increase was ensured in anti-HBs GMCs after the first booster dose vaccine when compared with the levels before the vaccination. A significant decreased correlation concerning anti-HBs GMCs was found in 60 children in T1-T6 (p=0.000, r -0.69) and a

significant increased correlation was found in 41 children in T6-T7 (p=0.000, r 0.73) and in T1-T7 (p=0.000, z 0.70). A significant relationship was observed concerning anti-HBs positive conversion rates in 60 children in T1-T6 (p=0.000, z -4.0, negative ranks=39, positive ranks=15, ties=6) and in 41 children in T6-T7 (p=0.000, z -4.8, negative ranks=3, positive ranks=32, ties=6) and in T1-T7 (p=0.001, z -3.2, negative ranks=6, positive ranks=29, ties=6).

Anti-HBs positive conversion rates after the 1st, 2nd and 3rd vaccination were lower in children who had been exposed to tobacco smoke and children with obesity that will not be fully significant (p>0.05). Anti-HBs positive conversion rates in T6 and T7 were revealed significantly higher in children with malnutrition than among the others (p=0.008, Z -2.56, U 60.5, p=0.03, Z -2.11, U 26.5).

When we compared the 81 children who had been tested after the first vaccination, anti-HBs positive conversion rates in T1 were found to be significantly lower in children whose anti-HBs titer was under 1 mIU/mL before the first vaccination than in the other group (p=0.01, Z -3.29, U 469). There was no difference for T6 and T7 between these groups (p>0.05).

DISCUSSION

To prevent HBV infection, the World Health Organization advocated HBV vaccination of all infants in 1992, first and universal vaccination by the end of 2013 (1). Turkey is a country which has an intermediate endemicity concerning HBV infection (5). Effective control of HBV transmission in regions with high and intermediate endemicity would not be possible without the vaccination of the most vulnerable groups of the population (6). The vaccine was included in the vaccination schedule in Turkey in 1998 (7).

Although there is no hesitation about hepatitis B vaccine being the most efficient way to prevent HBV infection, there are a few questions as to the duration of protection, the necessity of a booster dose and timing, and whether protection will continue if the anti-HBs titer fall below <10 mIU/mL (8-15).

Risk factors and efficient vaccination strategies have been developing concerning hepatitis B vaccine unresponsiveness which is seen in 1-15% of cases according to several studies (2,3,8,16). Several factors have been associated with nonresponse to hepatitis B vaccine. These factors include vaccine factors (e.g., dose, schedule, injection site) and host factors. Male gender, obesity, smoking, and chronic illness have been independently associated with unresponsiveness to hepatitis B vaccine (4). The Centers for Disease Control and Prevention have advised that individuals who do not respond to the first series of hepatitis B vaccine should complete a second three dose vaccine series. The second vaccine series should be given over the usual 0, 1, 6 month schedule (4). In this study, we have aimed to evaluate booster dose vaccine responses after using a 0, 1 and 6 month vaccine schedule among the children who were unresponsive to the primary hepatitis B vaccine and determine sensitive groups concerning vaccine response.

High rates of hepatitis B carriers (35%) were found among the children's families or first degree relatives. This situation may be seen as coincidental as indeed the prevalence of this disease in our country may well be related with genetic or ethnic factors (5,17-20).

In our study, none of the children were positive for HBsAg or anti-HBc antibodies or were reported to have clinical symptoms of HBV infection during the 8.8 years after primary HBV vaccination. It has been shown that vaccine induces active production of anti-HBs antibody accompanied by HBsAg specific immunological memory that provide continuous protection in the absence of antibody. These findings also confirm what has been demonstrated in other studies (11,12). Individuals whose anti-HBs levels decline to <10 mIU/mL may not be at risk of hepatic disease since they have HBsAg specific immunological memory. Following exposure to HBV, the presence of the immunological memory rapidly leads to a robust anamnestic response, which prevents acute disease and chronic infection (12).

Protective anti-HBs titers were supplied after the three dose vaccination for all of the children in our study and results were found to be high after the first booster dose (95.1%) and were consistent with other studies (Malaysia 94.0% and Germany 97.2%-99.6%) (9.22).

In our study, anti-HBs positive conversion rates in T1 were determined to be significantly lower in children whose anti-HBs titer was under 1 mIU/mL before the vaccination than the other groups. In fact, there was no difference in T6 and T7 between the groups. This situation has recently been studied in order to identify genetic reasons (17-19,23,24). We therefore believe that three dose booster vaccination is suitable for these children.

Studies have shown that the hepatitis B vaccination response is lower in obese children (25,26). Although statistical significance was not detected in our study, anti-HBs positive conversion rates after the 1st, 2nd and 3rd vaccinations were lower in obese children. It has been shown in other studies that hepatitis B vaccine response is influenced negatively in patients with malnutrition. In our study, anti-HBs positive conversion rates in T6 and T7 were seen to be significantly higher in children with malnutrition than the other group. We think that this result is associated with the immunity problems children with malnutrition often confront as well as technical problems during their vaccination (27). In our opinion, three dose booster vaccination is suitable for children with malnutrition.

Our study has limitations such as the small case group and the fact that the anti-HBs titer after the last vaccination could not be checked in the long term.

For children with low or undetectable anti-HBs titers after hepatitis B vaccination, several methods have been developed to overcome this unresponsiveness. The current chief counter measures include using more immunogenic epitopes or replacement vaccines, increasing the number of vaccinations and doses, changing the method of vaccination, and combining the vaccine with an adjuvant or immunoregulant (8,16,28-31). In our study, anti-HBs seroconversion rates and anti-HBs GMCs in T1 decreased rapidly in T6 after 5 months. Additionally, both anti-HBs seroconversion rates and anti-HBs GMCs in T6 after the third booster dose increased rapidly in T7. So, the significant difference about the increased aspect of seroconversion rate and GMCs between T1 and T7 and the rapid decrease in T6 despite two dose vaccination are related with reminding, anti-HBs titer before vaccination and the checking time of anti-HBs rather than the number of reminding doses (17,32,33).

In conclusion, high-rated protection (95.1%) is obtained after the first dose booster vaccination. When we examine the rapid decrease in T6 in contrast with two doses vaccination, it is thought that anti-HBs seroconversion rates and anti-HBs GMCs are related with reminding, anti-HBs titer before vaccination and the checking time of anti-HBs rather than the number of reminding doses. In our opinion, providing those children whose anti-HBs titer is under <1 mIU/mL and who have malnutrition with three dose vaccination is more suitable. Further studies are need to concerning this subject which include larger sample groups and long-term testing of antibody titers.

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