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Hepatit B Aşılama Sonrası Aşı Yanıtına Etki Eden Faktörlerin Değerlendirilmesi

Assessing the Factors Influencing Vaccine Response After Hepatitis B Vaccination

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ÖZ

Giriş: Hepatit B virusu(HBV) aşı ile önlenebilir. Bazı hastalarda uygun aşılama sonrası yeterli antikor yanıtı oluşmamaktadır. Bu çalışmada, aşı merkezimize başvuran HBsAg, Anti-HBc IgG ve Anti-HBs negatif olguların Hepatit B aşısına verdikleri aşı yanıtını ve bu yanıtı etkileyen faktörleri araştırmayı amaçladık.

Yöntem: Çalışmaya, 01/Mart/2021 ve 31/Ağustos/2024 tarihleri arasında başvuran, 18 yaş üstü, üç doz standart aşılamanın uygulandığı ve 3. dozdan 30 gün sonra Anti-HBs kontrolü bakılmış 170 kişi çalışmaya alındı. Olgulara ait demografik veriler ve aşı yanıtını etkileyebileceği düşünülen faktörleri hastane bilgi sistemi üstünden retrospektif olarak incelendi.

Bulgular: Çalışmaya alınan 170 kişiden 93 (%54.7)'ü erkek, yaş ortalamaları 42.02'idi. Aşılama sonrası olguların %87(n: 148)'sinde aşı yanıtı oluştuğu saptandı. Aşı yanıtı oluşmayan grubun ortalama yaşı 50.5 yıl, aşı yanıtı olan grubun yaş ortalaması 40.8 yıl olup anlamlı fark mevcuttu($p<0.001$). HIV ile yaşayan bireylerde aşı yanıtı %57.7 iken HIV negatif grupta %92.4 olup anlamlı farklılık mevcuttu ($p<0.001$). İmmünsüpresif tedavi kullanan bireylerde aşı yanıtı %40 iken, kullanmayan grupta %91.6 olarak anlamlı farklılık saptandı ($p<0.001$). Yapılan logistic regression analizinde, kişinin 50 yaşın üstünde olması 3.72 kat, HIV varlığı 40.73 kat, immünsüpresif tedavi alması 94 kat aşı yanıtsızlığı riskini arttırdığı saptandı.

Sonuç: 50 yaş üstü hastalarda, immünsüpresif ilaç kullananlarda ve HIV pozitif olanlarda aşı yanıtının daha düşük olabileceği değerlendirilmiştir.

Anahtar Kelimeler: hepatit B virüsü, anti-HBs testi, aşılama, aşı yanıtı

ABSTRACT

Objective: Hepatitis B virus(HBV) can be prevented with vaccination. Some individuals fail to elicit an adequate antibody response despite appropriate vaccination. In this study, we aimed to assess the vaccine response to the HBVvaccine in subjects who tested negative for HBsAg, Anti-HBc, and Anti-HBs at our vaccination center, and to identify the factors influencing this response.

Method: The study included 170 individuals over the age of 18 who visited our clinic between 01/March/2021 and 31/August/2024. All participants who received three doses of standard vaccination had their Anti-HBs levels checked 30 days after the third dose. Demographic data and potential factors influencing the vaccine response were analyzed retrospectively through the hospital information system.

Results: Of the 170 individuals included in the study, 93(54.7%) were male, with a mean age of 42.02 years. A vaccine response was observed in 87%(n=148) of the cases following vaccination. The mean age of the non-responsive group was 50.5 years, compared to 40.8 years in the responsive group($p<0.001$). The vaccine response rate was 57.7% in individuals living with HIV, compared to 92.4% in the HIV-negative group($p<0.001$). Among individuals on immunosuppressive therapy, the vaccine response was 40%, while it was 91.6% in those not on such therapy($p<0.001$). In logistic regression analysis, being over 50 years old increased the risk by 3.72 times, having HIV by 40.73 times, and receiving immunosuppressive therapy by 94 times.

Conclusion: It has been evaluated that the vaccine response may be lower in patients over 50 years of age, those using immunosuppressive drugs, and those who are HIVpositive.

Keywords: hepatitis B virus, anti-HBs test, vaccine, vaccine response

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INTRODUCTION

Hepatitis B virus (HBV) infection remains a major global cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (1). According to the World Health Organization (WHO) global hepatitis report, it is estimated that in 2022, 254 million people were living with chronic hepatitis B infection, with approximately 1.2 million new cases occurring each year. The same report estimates that hepatitis B is responsible for around 1.1 million deaths, the majority of which are due to cirrhosis and hepatocellular carcinoma (primary liver cancer) (2).

HBV is transmitted through contact with infected body fluids, such as blood, saliva, vaginal fluids, and semen. It can also be transmitted from mother to child. Hepatitis B infection can be prevented through the administration of a safe and efficacious vaccine. The World Health Organization (WHO) advises that all infants should receive the hepatitis B vaccine promptly after birth (within the first 24 hours), with a complete vaccination series consisting of three doses given at intervals of no less than four weeks. For individuals who respond to the vaccine, protection against hepatitis B lasts at least 20 years and likely for a lifetime (2).

However, some individuals fail to elicit an adequate antibody response despite appropriate vaccination. Factors that may contribute to a reduced vaccine response include advanced age, obesity, and various primary immune system disorders (such as defects in mannose-binding lectin, leukocyte adhesion deficiency, chronic granulomatous disease, common variable immunodeficiency (CVID), hyper-IgM syndrome, and DiGeorge syndrome), as well as chronic diseases (like essential hypertension) (3). Furthermore, diseases associated with immunosuppression (such as Type 1 diabetes mellitus (DM), Type 2 DM, and HIV/AIDS), along with the use of immunosuppressive agents (rituximab, systemic steroids, and monoclonal antibodies), have been documented to reduce vaccine response (4,5,6).

In this study, we aimed to investigate the vaccine response following three doses of hepatitis B vaccine in subjects who tested negative for HBsAg, anti-HBc IgG, and Anti-HBs at our vaccination center, as well as the factors influencing this response.

MATERIALS AND METHODS

This study was conducted with the approval of the Ethics Committee for Clinical Research at T.R.Health Scıences Unıversıty Hamıdiye Scıentıfic Research Ethıcs Commıttee (17.10.2024 - 24/582).

Laboratory results from 1,236 patients aged 18 years and older who presented to the vaccination clinic between March 1, 2021, and August 31, 2024, were retrospectively analyzed. The analysis was conducted utilizing clinical files and the hospital information system. Among these patients, 170 individuals who were initially negative for HBsAg, anti-HBc IgG, and Anti-HBs prior to vaccination were included in the study. Three doses of the standard hepatitis B vaccination regimen, which consisted of one intramuscular injection of 20 μg of recombinant hepatitis B vaccine, were administered to these participants, and their Anti-HBs levels were subsequently measured. A threshold of ≥ 10 IU/mL for Anti-HBs, assessed at least 30 days after the third vaccination dose, was established as indicative of a vaccine response.

Demographic characteristics of the patients, HBV serology results, vaccination rates, and vaccine responses among the vaccinated cohort were examined based on these 170 subjects. The detection of HBsAg, anti-HBc IgG, and anti-HBs markers was performed using EIA (the AXSYM-Abbott kit).

Statistical Analysis

Statistical analysis was conducted using IBM SPSS version 22. Descriptive statistics for numerical variables were presented as mean, standard deviation, minimum, maximum, median, and interquartile range, while categorical variables were expressed as frequency and percentage. The ratios between groups were compared using the χ^2 test. Comparisons of numerical variables between independent groups were performed using the Mann-Whitney U test due to the non-normal distribution of data. Statistical significance was investigated at a confidence level of 95% ($p<0.05$).

RESULTS

Out of the 170 individuals followed in our vaccination clinic, 93 (54.7%) were male. The average age of the cases was 42.02 years (ranging from 20 to 79). The demographic and clinical characteristics of the patients are summarized in Table 1.

Table 1. Demographic and Clinical Characteristics of the Cases (n=170)

		All patients n (%)
Gender	Female	77 (45.3)
	Male	93 (54.7)
Tip 2 DM		13 (7.6)
Essential Hypertension		18 (10.6)
Chronic Kidney Disease*		1 (0.6)
Anti-HCV (+)		1 (0.6)
HIV positivity		26 (15.3)
Use of immunosuppressive therapy		15 (8.8)
Hematological malignancy		1 (0.6)
Solid organ malignancy		-
Solid organ transplantation**		1 (0.6)

n: Number of Cases, DM: Diabetes Mellitus, HCV: Hepatitis C Virus, HIV: Human Immunodeficiency Virus
* Hemodialysis and peritoneal dialysis patients were excluded from the study.
** Renal transplant was performed.

It was determined that 87% (n:148) of the cases developed a vaccine response after the standard 3-dose vaccination. All 22 individuals who did not respond to the vaccine received a second series of vaccinations (an additional 3 doses at 0, 1, and 6 months), with 31.8% (n:7) of them developing a response after the second series.

When assessing the factors influencing vaccine response, no significant

differences were observed between genders. The mean age of the non-responsive group was 50.5 years, in contrast to 40.8 years in the responsive group, indicating a statistically significant difference ($p < 0.001$).

No significant difference in vaccine response was found in individuals with type 2 DM and Essential Hypertension ($p > 0.05$).

In individuals living with HIV, the vaccine response rate was 57.7%, compared to 92.4% in the HIV-negative group, demonstrating a statistically significant difference ($p < 0.001$) (Table 2).

Table 2: Comparison of Factors Affecting HBV Vaccine Response

		HBV vaccine response n (%)		*p* value
		Yes 148 (87)	**No 22 (13)**	
Age, sd		40,8 ± 13,7	50,5 ± 8,4	**<0,001**
Gender	Female	69 (89,6)	8 (10,4)	0,367
	Male	79 (84,9)	14 (25,1)	
Tip 2 DM	Yes	12 (92,3)	1 (7,7)	>0,05
	No	136 (86,6)	21 (13,4)	
Essential Hypertension	Yes	15 (83,3)	3 (16,7)	0,708
	No	133 (87,5)	19 (12,5)	
HIV	Positive	15 (57,7)	11 (42,3)	**<0,001**
	Negative	133 (92,4)	11 (7,6)	
Immunosuppressive therapy	Yes	6 (40)	9 (60)	**<0,001**
	No	142 (91,6)	13 (8,4)	

n: number of cases, DM: Diabetes Mellitus, HIV: Human Immunodeficiency Virus, HBV: Hepatitis B Virus

Among those receiving immunosuppressive therapy, the vaccine response rate was 40%, while it was 91.6% in individuals not undergoing such therapy, a difference that was statistically significant ($p < 0.001$).

Logistic regression analysis indicated that being over the age of 50 increased the risk of non-responsiveness by 3.72 times, the presence of HIV elevated the risk by 40.73 times, and receiving immunosuppressive therapy heightened the risk by 94 times.

DISCUSSION

Hepatitis B virus (HBV) infection is associated with significant mortality and morbidity, primarily due to its progression to cirrhosis and hepatocellular carcinoma. Approximately 1.2 million new infections are reported annually, leading to an estimated 1.1 million deaths. Despite the existence of a safe and effective vaccine against hepatitis B, the primary challenges remain as inadequate vaccination coverage and insufficient vaccine responses among vaccinated individuals. This study aimed to investigate the factors influencing vaccine response in 170 participants who received three doses of the standard HBV vaccine.

In our analysis, the antibody response rate following HBV vaccination was found to be 87%, aligning with findings reported in the literature. A majority of patients exhibited a positive vaccine response following vaccination. A significant correlation was identified between age and vaccine response rates. The mean age of individuals demonstrating an HBV antibody response was significantly lower. Those over 50 years old exhibited a 3.72-fold increased risk of having an inadequate anti-HBs response, as indicated by logistic regression analysis. In the study conducted by Joukar F et al., it was reported that healthcare workers aged over 50 had approximately a fivefold higher risk (OR = 4.48) of insufficient anti-HBs response when compared to their counterparts under 30 years of age(7). Our findings, consistent with existing literature, indicate that the antibody response may decline in older age groups.

Moreover, it is well-established that females generally develop higher neutralizing antibody titers following vaccinations. In a study by Trevisan et al., female participants demonstrated a significantly higher antibody response to HBV vaccination (8). In our study, the vaccine response rate among females was 89.6%, in contrast to 84.6% for males. Although the vaccine response was numerically greater among females, this difference did not achieve statistical significance.

The Centers for Disease Control and Prevention recommends that all unvaccinated adults with diabetes (type 1 and type 2) aged 19 to 59 years receive vaccination against hepatitis B as soon as possible after a diabetes diagnosis (9). In previous studies, the impact of comorbidities on immune response was found to be statistically insignificant (10, 11). In our study, the effects of type 2 DM and essential hypertension on vaccine response were examined, and no statistically significant results were found.

National and international guidelines advise hepatitis B vaccination for all HIV-positive individuals who are neither chronically infected with HBV nor immune to the virus (12). Although the guidelines have been updated over the years, there is still no consensus regarding the timing and dosing of vaccination. At our vaccination clinic, we have followed evolving guidelines over the years to recommend vaccinations for our patients. All patients included in the study were vaccinated with the standard dose of the hepatitis B vaccine at 0, 1, and 6 months. Previous studies have reported that the vaccine response rate in individuals living with HIV after standard hepatitis B vaccination ranges from 17% to 86.6% (13, 14). In our study, the response rate among HIV patients after the initial vaccination series was found to be 57.7%. It has been emphasized that detectable HIV-RNA levels and low CD4+ T lymphocyte counts influence vaccine response. A CD4+ T lymphocyte count of <200 cells/mm³ has been associated with a reduced vaccine response in HIV patients (15, 16). Additionally, changes in vaccination schedules have been shown to affect vaccine responses (17). Detectable HIV-RNA levels represent another factor negatively impacting vaccine response (11, 18). In our study, among the 11 HIV-positive individuals who did not exhibit a vaccine response after the first series, 7 had CD4+ T lymphocyte counts ranging from 200 to 350 cells/mm³, while 4 had CD4+ T lymphocyte counts of <200 cells/mm³. The low percentage of CD4+ cells was considered potentially related to the poor vaccine response. These 11 cases subsequently received a second series of three standard doses of the HBV vaccine, resulting in a response in 5 individuals. Upon examining these 5 cases, it was noted that 2 had CD4+ cell counts >200 cells/mm³, while the other 3 maintained

CD4+ cell counts between 200 and 350; however, the undetectable HIV-RNA levels during the second series of vaccination may have contributed to an improved vaccine response.

Some studies have reported that HCV positivity, particularly leading to cirrhosis, reduces the HBV vaccine response. Among the cases included in our study, only one patient was HCV positive, and this individual had non-cirrhotic chronic HCV infection. Immunity against HBV was achieved after three doses of vaccination. Due to the insufficient number of patients, statistical analysis could not be performed (19).

In our study, we determined that the HBV vaccine response was significantly reduced in patients using immunosuppressive medications. Logistic regression analysis on patients receiving immunosuppressive drugs revealed that the use of immunosuppressive therapy increased the risk of non-responsiveness to vaccination by 94-fold. While there is a lack of comprehensive studies examining vaccine responses in immunosuppressed patient groups, it has been noted that therapies used in inflammatory bowel diseases specifically reduce vaccine responses (20). A small proportion of our patients, 8.8% (n=15), were receiving immunosuppressive treatment. We believe that additional research with a larger group of patients is required in this field.

CONCLUSION

The majority of cases developed a vaccine response after the standard 3-dose vaccination. It was observed that patients over the age of 50 and those receiving immunosuppressive drugs might have a lower vaccine response. Vaccination is extremely important for individuals living with HIV who are HBV seronegative. Our study concluded that the optimal timing for vaccination is indicated by a CD4+ T lymphocyte count greater than 200 cells/mm³ and suppressed viral load.

Ethics Committee Approval: This study was conducted with the approval of the Ethics Committee for Clinical Research at T.R.Health Scıences Unıversıty Hamıdiye Scıentıfic Research Ethıcs Commıttee (17.10.2024 - 24/582).

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