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Evaluation of Antibody Response and Side Effects Related to the Number of Inactive and mRNA Vaccine Doses Against COVID-19 in Healthcare Workers

Sağlık Çalışanlarında COVID-19`a Karşı İnaktif ve mRNA Aşılanma Sonrası Doz Sayısına Bağlı Antikor Yanıtı ve Yan Etkilerin Değerlendirilmesi

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ABSTRACT

Introduction: *Studies are showing that a high antibody response increases the protection against variants in the fight against the COVID-19 pandemic. In this study, we aimed to investigate the relationship between antibody response and side effects based on the number of doses administered to healthcare workers who were vaccinated against COVID-19.*

Materials and Methods: *Healthcare workers, who were vaccinated with two doses of BNT162b2 (Group 1), a single dose of BNT162b2 following two doses of CoronaVac (Group 2), or two doses of BNT162b2 following two doses of CoronaVac (Group 3), were randomly assigned to this study. Serum samples were taken from the participants 30 ± 2 days after the last vaccination date, and the SARS-CoV-2 anti-spike S1 RBD IgG test was administered to these samples. A questionnaire was conducted detailing the demographics of the patients as well as their post-vaccination complaints. The results were analyzed statistically. Analysis results with a p-value of <0.05 were considered significant.*

Results: *A total of 179 healthcare professionals with a mean age of 41.7 ± 10.6 years were included in our study. Of the studied samples, 95.5% (n= 171) were interpreted as anti-spike S1 RBD IgG seropositive. Positivity rates and mean antibody levels were 93.2%, 95.9%, 97.8%, and 107.4 ± 117.1, 152.7 ± 108.5, 201.4 ± 114.9 (AU/mL) for Group 1, Group 2, and Group 3, respectively (p< 0.05). In general, no significant differences in antibody response were seen based on gender or age. However, a significant correlation was found between the occurrence of vaccine-related side effects and antibody titer (p< 0.001). The most common side effect was pain in the area where the vaccine was administered, with a rate of 77.4% (n= 48). More vaccine-related side effects were reported in participants under the age of 40 and in female healthcare workers.*

Conclusion: *We believe that booster doses are effective for increasing the immune response and thus protecting against COVID-19. More extensive research should be conducted to confirm the link between the occurrence of vaccine-related side effects and antibody titer. Furthermore, studies on the safety of increasing the number of vaccine doses are required.*

Key Words: *COVID-19; Vaccine; Anti-spike s1 rbd igg; Number of doses; Antibody response*

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ÖZ

Sağlık Çalışanlarında COVID-19`a Karşı İnaktif ve mRNA Aşılanma Sonrası Doz Sayısına Bağlı Antikor Yanıtı ve Yan Etkilerin Değerlendirilmesi

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Giriş: *COVID-19 salgınına karşı mücadelede antikor yanıtın yüksek olmasının varyantlara karşı koruyuculuğu artırdığına yönelik çalışmalar mevcuttur. Bu çalışmada COVID-19'a karşı aşılanmış sağlık çalışanlarında aşı sonrası doz sayısına bağlı oluşan antikor yanıtı ve yan etki ilişkisini değerlendirmeyi amaçladık.*

Materyal ve Metod: *Çalışmaya randomize olarak sadece iki doz BNT162b2 ile aşılanmış olanlar (Grup 1) ve iki doz CoronaVac sonrası tek doz (Grup 2) veya iki doz (Grup 3) BNT162b2 ile aşılanmış olanlar dahil edildi. Katılımcılardan serum örnekleri son aşılanma tarihinden itibaren 30 ± 2 gün sonra alındı ve örneklere SARS-CoV-2 anti-spike S1 RBD IgG testi çalışıldı. Hastaların demografik verileri ve aşı sonrası oluşan şikayetleri ile ilgili anket formu dolduruldu. Sonuçlar istatistiksel olarak analiz edildi, p< 0.05 değeri anlamlı kabul edildi.*

Bulgular: *Çalışmamıza yaş ortalaması 41.7 ± 10.6 olan toplamda 179 sağlık çalışanı dahil edildi. Çalışılan örneklerin %95.5'i (n= 171) anti-spike S1 RBD IgG seropozitif olarak yorumlandı. Gruplara göre pozitiflik oranları ve ortalama antikor düzeyleri sırasıyla Grup 1, Grup 2, Grup 3; %93.2, %95.9, %97.8; 107.4 ± 117.1, 152.7 ± 108.5, 201.4 ± 114.9 idi (p< 0.05). Genel olarak cinsiyet ve yaşa göre antikor yanıtında anlamlı bir farklılık tespit edilmedi. Ancak aşıya bağlı yan etki oluşumu ile antikor titresi arasında anlamlı bir ilişki bulundu (p< 0.001). En sık görülen yan etki %77.4 (n= 48) oranında aşı yapılan bölgede gelişen ağrı şikayetiydi. Katılımcılardan 40 yaş altı olanlarda ve kadın sağlık çalışanlarında daha fazla aşıya bağlı yan etki bildirildi.*

Sonuç: *COVID-19'a karşı immün yanıtı ve dolayısıyla koruyuculuğu artırmak için hatırlatma dozlarının yapılmasının etkili olduğunu düşünmekteyiz. Aşıya bağlı yan etki oluşumu ile antikor titresi arasındaki ilişki daha kapsamlı çalışmalarla pekiştirilmelidir. Bunun yanında aşı doz sayısının artırılmasının güvenliği hakkında çalışmalara ihtiyaç vardır.*

Anahtar Kelimeler: *COVID-19; Aşı; Anti-spike s1 rbd igg; Doz sayısı; Antikor yanıt*

INTRODUCTION

The Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), spread rapidly around the world since the day it was identified and caused a pandemic[1]. According to the data reported by the World Health Organization (WHO) on 09.03.2022, there were approximately 480 million confirmed cases and 6.1 million deaths. Approximately 11 billion doses of COVID-19 vaccines have been administered worldwide[2]. Vaccination is the most cost-effective and reliable method for combating infectious diseases, such as the SARS-CoV-2 pandemic[3]. In this context, different types of vaccines have been developed and are still being developed by many research laboratories all around the world. Inactive virus vaccines, recombinant viral vector vaccines, live-attenuated virus vaccines, particle virus-like protein (VLP) vaccines, DNA vaccines, and mRNA vaccines are examples of these vaccines[4,5]. Currently, the most commonly used types of vaccine in the world and our region are inactivated vaccines and mRNA vaccines. Vaccines were first administered to health workers in our region per the vaccination policy of our country and the majority received two doses of the CoronaVac (Sinovac Biotech, China) inactivated virus vaccine. The third dose was given six months later, and a fourth dose was optional. At this point, in addition to the CoronaVac vaccine, an mRNA vaccine, BNT162b2 (Pfizer-BioNTech), was available as a vaccine option. Several studies have been published in the literature to investigate the antibody response to inactive or mRNA vaccination[6,7]. However, studies are insufficient since different vaccinations and doses are used. The purpose of this study was to investigate the differences in

antibody responses that occur following different doses and types of vaccination in health workers.

MATERIALS and METHODS

Study Design

This was a prospective study that included healthcare workers with various immunization statuses in a single-center, tertiary hospital.

Study Group

A total of 179 healthcare professionals working at Mersin University Medical Faculty Hospital, who were aged between 18-65, and had no previous history of COVID-19 were included in this study. Individuals who were receiving immunosuppressive treatment were not included in this study. Serum samples were collected from volunteer healthcare workers to form three randomized groups. Group 1 (n= 59) consisted of those who received only two doses of mRNA (BNT162b2) vaccine, Group 2 (n= 74) of those who received a single dose of mRNA vaccine following two doses of inactive (CoronaVac) vaccine, and Group 3 (n= 46) of those who received two doses of mRNA vaccine following two doses of inactive vaccine.

Sample Collection

Blood samples were collected from healthcare workers at Mersin University Medical Faculty Hospital who voluntarily participated in this study 30 ± 2 days following their last vaccination. The blood samples were centrifuged at 4000 rpm for 10 minutes without waiting to separate the serums, which were then placed in 1.5 mL vials and stored in a deep freezer at -20°C until anti-spike IgG was detected.

Detection of Anti-spike IgG

Access SARS-CoV-2 IgG II (Beckmann Coulter, USA) test, a chemiluminescent immunoassay method with paramagnetic particles, was used for the detection of SARS-CoV-2 anti-spike S1 RBD IgG. The Access SARS-CoV-2 IgG II assay aims to detect the antibody response specific to the receptor binding site (RBD) of the S1 protein. The clinical sensitivity and specificity of this test were reported by the manufacturer as 100% (>18 days) and 99.8%, respectively.

Interpretation of Results and Reporting

System software computed the test results automatically. The collected results were analyzed in accordance with the manufacturer's recommendations. Access SARS-CoV-2 IgG test results of <10 AU/mL were interpreted as negative, and results ≥10 AU/mL were interpreted as positive.

Statistical Analysis

All obtained data were analyzed using SPSS 20.0 (IBM, Armonk, NY, USA) and Excel (Microsoft Office Professional Plus 2016) software. Student's t-test was used to determine the 95% confidence interval, and the Kolmogorov-Smirnov test was used for the normality analysis of the parameters. The Chi-square test and Mann-Whitney U test were used to compare the differences between groups. Spearman analysis was used to evaluate the correlation of outcome values with ordinal variables. The statistical significance level was accepted as $p< 0.05$.

RESULTS

The mean age of the healthcare workers included in our study was 41.7 ± 10.6 (min-max; 18-63), 58.7% (n= 105) were female and 41.3% (n= 74) were male. In this study, SARS-CoV-2 IgG antibody response was positive in 95.5% (n= 171) of the serum samples of 179 healthcare workers. On the other hand, eight (4.5%) samples had negative results. SARS-CoV-2 IgG antibody positivity rate was found as 93.2%, 95.9%, and 97.8% for Group 1, Group 2, and Group 3, respectively. The mean anti-spike S1 RBD IgG titer of antibody-positive samples was calculated as 150.3 ± 118.0 AU/mL. The mean antibody titers for Group 1, Group 2, and Group 3 were found as 107.4 ± 117.1, 152.7 ± 108.5, and 201.4 ± 114.9, respectively ($p< 0.05$). According to these data, Group 3, who received four doses of vaccine, had the highest positivity rate and antibody titer among all groups (Figure 1). Antibody levels and positivity rates of the individuals included in our study did not show a statistically significant difference based on age and gender (Table 1). No significant relationship was found

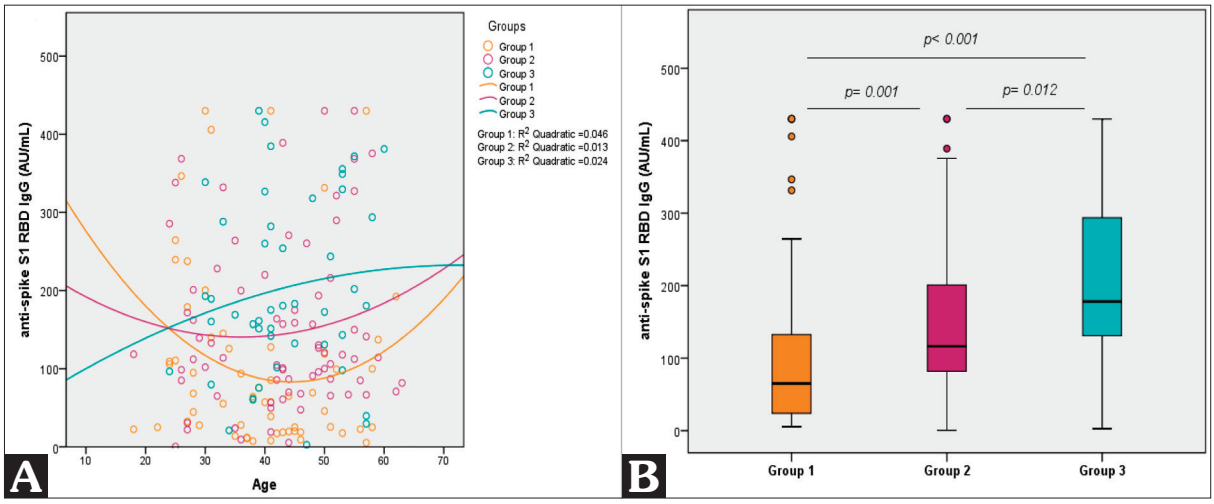

Figure 1. A. Antibody level-age correlation graph according to vaccine groups. **B.** Boxplot distribution of antibody levels according to vaccine groups (Mann-Whitney U test was used as statistical analysis).

Table 1. Analysis of SARS-CoV-2 S1 RBD IgG levels according to different groups

Type of vaccine (n)	Group 1 BNT162b2 (2)	p	Group 2 CoronaVac (2) BNT162b2 (1)	p	Group 3 CoronaVac (2) BNT162b2 (2)	p	Total	p
Characteristics	mean ± SD (CI 95%)		mean ± SD (CI 95%)		mean ± SD (CI 95%)		mean ± SD (CI 95%)	
Age (min-max)	(18-62)		(18-63)		(24-60)		(18-63)	
≤40	121.8 ± 115.9 (83.1-165.4)	0.111	153.1 ± 106.7 (112.6-194.3)	0.732	191.4 ± 121.2 (139.3-248.8)	0.540	149.8 ± 116.9 (123.6-177.5)	0.934
>40	91.6 ± 118.5 (53.6-140.7)		152.4 ± 110.6 (122.5-185.5)		208.5 ± 112.0 (167.2-250.1)		150.6 ± 119.2 (130.4-174.2)	
Gender								
Female	106.8 ± 97.3 (73.0-142.7)	0.533	157.3 ± 108.3 (127.0-187.4)	0.680	216.1 ± 112.8 (176.2-256.6)	0.300	158.2 ± 113.3 (136.2-180.6)	0.111
Male	108.2 ± 139.0 (58.7-166.6)		145.8 ±110.4 (105.6-187.0)		176.4 ± 117.5 (117.7-236.0)		139.1 ± 124.3 (109.6-168.4)	
Side effect								
No	95.9 ± 118.4 (63.4-132.8)	**0.030**	133.9 ± 102.8 (104.7-165.2)	**0.021**	169.5 ± 108.0 (126.5-216.9)	**0.046**	127.2 ± 112.5 (106.8-147.9)	**<0.001**
Yes	141.3 ± 110.1 (90.4-197.6)		187.3 ± 112.4 (145.7-231.8)		239.4 ± 113.6 (193.8-288.0)		193.8 ± 116.5 (165.7-224.0)	
Total	107.4 ± 117.1 (77.4-135.6)		152.7 ± 108.5 (127.5-178.5)		201.4 ± 114.9 (168.8-234.4)		150.3 ± 118.0 (133.7-168.6)	**<0.05**

SD: Standard deviation, CI: Confidence interval.

between the change in antibody titers and age ($r_{spearman}$= 0.047, p= 0.530) (Figure 1). However, a significant positive correlation was detected when the relationship between the number of doses and the antibody titer was analyzed ($r_{spearman}$= 0.367, p< 0.001).

Healthcare workers who developed vaccine-related side effects were 34.6% (n= 62). The most common side effect was pain at the injection site with a ratio of 77.4% (n= 48). Other side effects included weakness/fatigue in 24.2% (n= 15), headache in 21.0% (n= 13), bone/

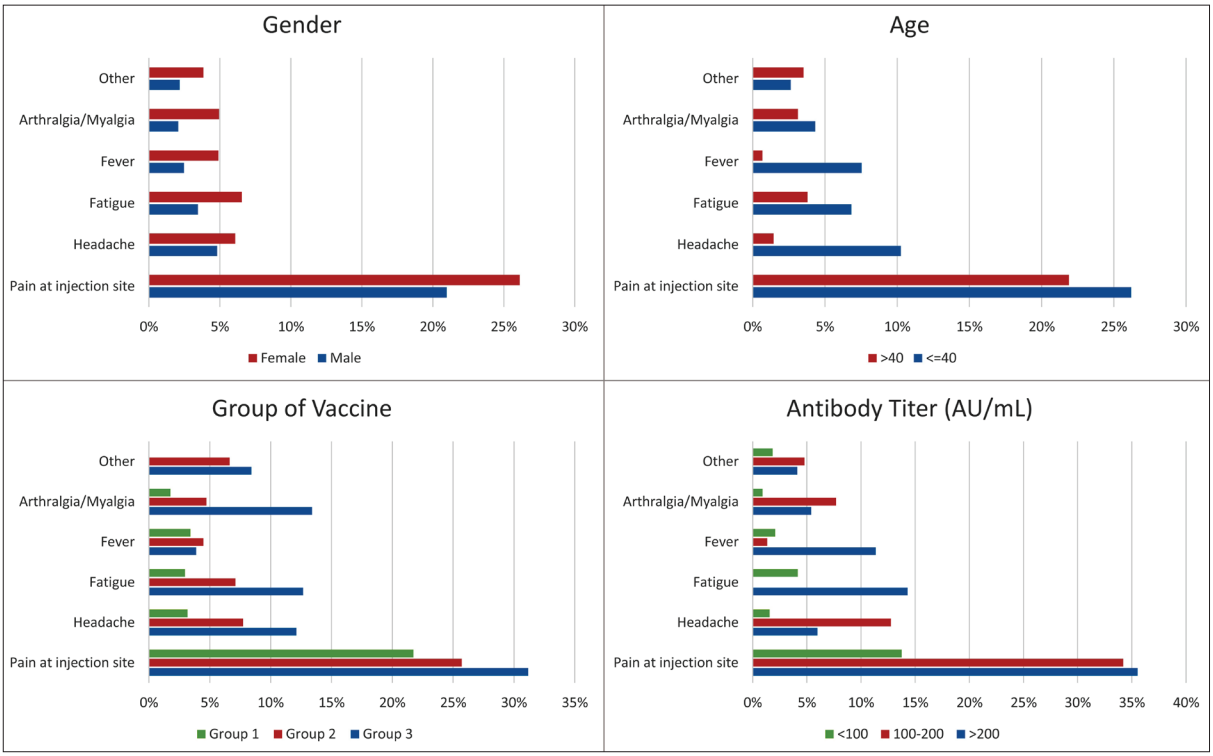

Figure 2. Percentage frequency of side effects due to COVID-19 vaccine according to different variables.

joint pain in 17.7% (n= 11), fever in 11.3% (n= 7), and other local and systemic side effects in 14.5% (n= 9) (Figure 2). Group 3 experienced the most vaccine-related side effects with a rate of 45.7%. When we analyzed the relationship between the antibody titer and the occurrence of side effects, it was observed that the occurrence of side effects was increased significantly in people with high antibody titer (Table 1). Although more vaccine-related side effects were reported in women than men (40% vs 27%; p= 0.072) and in individuals aged ≤40 years than those >40 years of age (41.3% vs 29.8%; p= 0.110), these differences were not statistically significant.

DISCUSSION

Despite the extensive measures taken to control the pandemic around the world, the impact of SARS-CoV-2 persists by emerging new variants that increase the rate of transmission. Neutralization studies have also been carried out by researchers against novel variants that have occurred or are likely to occur. According to these studies, increasing the number of vaccine doses is believed to boost the efficacy against variants[8,9]. However, there can be variability in efficacy depending on the type of vaccines and the demographic characteristics of the individuals. It has been reported that the neutralization levels are closely related to the level of antibodies that are formed against RBD in the S1 region of the S protein of the virus[10,11].

The mean positivity rate of the SARS-CoV-2 antibody (95.5%) in all vaccinated groups in our study was similar to other studies in the literature[6,12,13]. When compared to vaccination with only two doses of BNT162b2, vaccination with a single dose or two doses of BNT162b2 following two doses of CoronaVac produced better results in terms of both antibody positivity and antibody levels. This supports the view that increasing the number of doses and administering a booster dose will increase neutralization and hence be effective against both current and future SARS-CoV-2 variants. In addition, it has been reported in studies that the antibody response obtained after vaccination with BNT162b2 is higher than after vaccination with CoronaVac[14]. In

our study, those who were vaccinated with a single dose of BNT162b2 following two doses of CoronaVac had higher antibody levels than those who were vaccinated with two doses of BNT162b2. This demonstrates that following inactive vaccines with a booster dose of mRNA vaccines improves the immune response's low efficiency. This finding is supported by a few studies in the literature[15,16].

Zhang et al. found that individuals who received two doses of BNT162b2 + CoronaVac heterologously had stronger immunity than those who received two doses of homologous CoronaVac vaccine, and they argued that the combination vaccine strategy is safe[17]. In another study, they found that a dose of the BNT162b2 booster vaccine improved protection against the disease after two doses of CoronaVac, especially for the elderly[18]. Similar to this study, Zuo et al. found that booster dose mRNA vaccination after inactivated vaccine significantly increased antibody response. They also stated that heterologous vaccination significantly increased the specific memory B and T cell response compared to homologous mRNA vaccination[16].

In general, there was no statistically significant difference in antibody levels based on gender or age. However, antibody response to only two doses of the BNT162b2 vaccine was found to be higher in individuals under 40 years of age. The immune system's response is expected to decline as getting older, and this decline can be restored with booster doses. It was observed that increasing the number of vaccine doses or reminder doses increased the antibody response in favor of women. Although we did not find sufficient data in the literature, researchers found a significant antibody response inversely proportional to age after a single dose vaccination, similar to our study, when they analyzed the results based on age and gender. However, this difference became insignificant with increasing doses and durations. Similarly, when an analysis based on gender was performed, no significant difference in antibody response was seen between female and male groups in a single-dose vaccination, but a statistically significant difference was shown in favor of females in the second dose vaccination. However, this difference lost statistical significance on the 45th day after vaccination and at the subsequent analysis dates[19]. This provides evidence that the early immune response to second or booster doses may be higher in females. However, this evidence needs to be supported by more comprehensive studies.

In our study, the rate of side effects, described as giving discomfort, except for local and mild symptoms related to the vaccine, was 34.6%. In the literature, the incidence of side effects against different COVID-19 vaccines varies. Generally, the most common symptom in these studies was local effects at the administration site similar to our study[20,21]. When we look at the vaccine-related side effects between the groups, it has been observed that more side effects occur in women and individuals under the age of 40. Besides, it was observed that the incidence of side effects increased with the increasing number of vaccine doses. In our analysis, a significant relationship between the antibody level and the occurrence of side effects was found. In a study by Imai et al. about the effect of disease severity on antibody response; it has been observed that lower values in antibody seroconversion occur in patients with mild disease than those with severe disease[22]. We do not have enough evidence to associate this situation with the side effects of the vaccine. However, the frequency of vaccine-related side effects was found to be higher in the younger age group and female gender, similar to our study, but this situation could not be associated with antibody titer[23]. Since the degree of discomfort due to the side effects of the vaccine is not an objective situation and there can be different dynamics between individuals, it was considered inappropriate to evaluate vaccine-related side effects as a one-to-one immune response marker.

In this study, measuring the antibody levels of the participants at different periods before the vaccination and during the follow-up could provide a more effective evaluation of the results. However, a limited number of examples could be studied due to budget constraints.

CONCLUSION

In our study, antibody levels against SARS-CoV-2 were analyzed according to different vaccination status. In conclusion, it has been shown with the data we obtained in this study that increasing the number of doses increases the level of antibodies regardless of gender and age. Therefore, it is believed that booster doses may be effective in protecting against active variants and new SARS-CoV-2 variants that may occur in the future. However, more extensive clinical studies are needed to better understand the effects of increasing the number of doses in SARS-CoV-2 vaccination.

ETHICS COMMITTEE APPROVAL

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Mersin University Clinical Research Ethics Committee (Date: 15/12/2021 and Decision No: 2021/769). Written informed consent was obtained from the participants included in the study.

CONFLICT of INTEREST

The authors have no relevant financial or non-financial interests to disclose.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: TB, STÜ, GA

Analysis/Interpretation: All of authors

Data Collection or Processing: All of authors

Writing: All of authors

Review and Correction: All of authors

Final Approval: All of authors

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