RESEARCH ARTICLE / ARAŞTIRMA

DOI: 10.4274/mjima.galenos.2023.2023.22
Mediterr J Infect Microb Antimicrob 2023;12:22
Erişim: http://dx.doi.org/10.4274/mjima.galenos.2023.2023.22

Evaluation of Point-of-care and Traditional ELISA Techniques for the Detection of Anti-SARS-CoV-2 IgG Antibodies in Individuals Vaccinated Against COVID-19

COVID-19 Aşısı Olan Bireylerde Anti-SARS-CoV-2 IgG Antikorlarının Ölçümünde Hasta Başı ve Geleneksel ELISA Yöntemlerinin Değerlendirilmesi

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Abstract

Introduction: Coronavirus disease-2019 (COVID-19) has affected more than 676 million people till date, and 6,881,955 people have died from the disease as of March 28, 2023. Understanding the immunopathogenesis of the disease has led to more vaccine studies. The Comirnaty and CoronaVac vaccines are used in our country. The role of serology tests in the interpretation of protective and sustained immunity remains controversial after vaccines. However, serological testing is part of epidemiology and is essential for understanding the immunity against Severe acute respiratory syndrome-Coronavirus-2. We aimed to determine the antibody titers after vaccination and its effect on immunity, which could lead to new studies.
Materials and Methods: Two traditional enzyme-linked immunosorbent assay (ELISA) techniques (Euroimmune and Genzbio Covel) and one point-of-care (POC) method (Genz-Pro) were used in our study for detecting antibodies in vaccinated individuals.
Results: A total of 84 individuals were included in our study. The results obtained using the Genz-Pro test were evaluated according to the vaccine status; the positive antibody detection rate was significantly higher in Comirnaty-vaccinated patients than in CoronaVac-vaccinated individuals. The Spearman's correlation coefficient demonstrated a positive correlation between the two ELISA techniques.
Conclusion: The POC ELISA can quantify IgG seroconversion after COVID-19 vaccination with rapid and multiple measurements without sample accumulation. Thus, the POC ELISA can be used in COVID-19 services and outpatient clinics during post-vaccination follow-up to determine the performance of vaccines.
Keywords: Point-of-care systems, COVID-19 testing, antibodies, serologic tests

Öz

Giriş: Koronavirüs hastalığı-2019 (COVID-19) şu ana kadar 676 milyondan fazla insanı etkilemiş olup 28 Mart 2023 tarihi itibariyle 6.881.955 kişi bu hastalık nedeniyle kaybedilmiştir. Hastalığın immünopatogenezinin anlaşılması, aşı çalışmalarının hızlanmasına neden olmaktadır. Ülkemizde Comirnaty ve CoronaVac aşıları kullanılmaktadır. Koruyucu ve sürekli bağışıklığın yorumlanmasında aşılardan sonra seroloji testlerinin yapılmasının rolü tartışmalı olmaya devam etmektedir. Bununla birlikte, serolojik testler epidemiyolojinin bir parçasıdır ve Şiddetli akut solunum sendromu-Koronavirüs-2'ye karşı bağışıklığı anlamak için gereklidir. Bu makale aşılama sonrası oluşan antikorların ölçümü ve bağışıklığa etkisi hakkında fikir verebilir ve yeni çalışmalara öncülük edebilir.
Gereç ve Yöntem: Aşılanmış bireylerde antikor tespiti için çalışmamızda kullanılan iki geleneksel enzime bağlı immünosorbent testi (ELISA) (Euroimmune ve Genzbio Covel) ve bir hasta başı (POC) yöntemi (Genz-Pro) kullanıldı.

Cite this article as: Toygar Deniz M, Sayan M, Akhan S, Karaca E. Evaluation of Point-of-care and Traditional ELISA Techniques for the Detection of Anti-SARS-CoV-2 IgG Antibodies in Individuals Vaccinated Against COVID-19. Mediterr J Infect Microb Antimicrob. 2023;12:22.

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Received/Geliş Tarihi: 10.04.2023 **Accepted/Kabul Tarihi:** 23.08.2023

Published: 21.09.2023

Öz

Bulgular: Çalışmamıza 84 kişi dahil edildi. Genz-Pro ile elde edilen sonuçlar aşı durumuna göre değerlendirildi; pozitif antikor saptama oranı, Comirnaty ile aşılanmış hastalarda önemli ölçüde daha yüksekti. Ayrıca, Spearman'ın korelasyon katsayıları, iki ELISA tekniği arasında pozitif bir korelasyon gösterdi.
Sonuç: Bulgularımız, POC ELISA'nın numune birikimi olmadan hızlı ve çoklu ölçümlerle COVID-19 aşılamasından sonra IgG serokonversiyonunu ölçebildiğini göstermektedir. POC ELISA, aşıların performansını ölçmek için aşılama sonrası takipte COVID-19 servislerinde ve polikliniklerde kullanılabilir.
Anahtar Kelimeler: Hasta başı sistemleri, COVID-19 testi, antikorlar, serolojik testler

Introduction

The novel coronavirus was first detected in December 2019 in Wuhan, China, and declared a pandemic on March 11, 2020[1]. Coronavirus disease-2019 (COVID-19) has affected more than 676 million people till date, and 6,881,955 people have died from the disease as of March 28, 2023[2]. In Turkey, nearly 18 million people have been diagnosed with COVID-19 so far[3]. Despite the progress in the treatment and vaccines for COVID-19, the biggest challenge in the prevention of the pandemic is the variants emerging as a result of mutations in the Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) structure, which is the causative agent of COVID-19. Globally, the spread of Delta, which has been more common than the Alpha, Beta, and Gamma variants, has continued to decline. However, currently, the more contagious variant Omicron is increasing in incidence[4].

SARS-CoV-2, which belongs to the *Coronaviridae* family, is a single-stranded, positive-sense, RNA virus that has exhibited high genetic diversity since its first emergence[5]. Both humoral and cell-mediated immune responses are reportedly protective against COVID-19[6]. The S and N proteins of SARS-CoV-2 are the most immunogenic part of the virus, which induces IgG production. However, the humoral immune response is short-lived. Monoclonal antibodies against the binding domain of the virus can inhibit SARS-CoV-2 infection[7]. The use of monoclonal antibodies in the early period reportedly reduces mortality, just as in other viral infections during the early treatment stage[8]. Furthermore, specific T-cell responses against SARS-CoV-2 provide long-term protection, and a potent T-cell reactivity is associated with a high production of neutralizing antibodies[9].

Understanding the disease immunopathogenesis has led to the acceleration of vaccine studies. Coronavirus disease-2019 vaccines are categorized as protein subunits, viral non-replicated and replicated vector vaccines, inactivated virus vaccines, and DNA or RNA-based vaccines[10]. The inactivated coronavirus vaccine CoronaVac (Sinovac Biotech, Beijing, China) and mRNA-based virus vaccine Comirnaty (BNT 162b2; BioNTech, Fosun Pharma, Pfizer, NY, USA) (previously named BioNTech, Pfizer) are used in our country. A total of 51,487,225 people have received the two-dose vaccine scheme so far, with a vaccination rate of 82.9%[3]. However, viral variants have emerged due to mutations in the SARS-CoV-2 structure, resulting in strains that are immune to the vaccine or are more contagious and preventing the end of the pandemic.

The role of serology tests in the interpretation of protective and sustained immunity remains controversial. The U.S. Center for Disease Control and Prevention does not recommend measuring postvaccination titers for assessing immunity to COVID-19[11]. However, serological testing is a part of epidemiology and is essential for understanding the immunity against SARS-CoV-2. There are several antibody tests available in the market. Enzyme-linked immunosorbent assay (ELISA) is a plate-based assay in which the microtiter wells are coated with SARS-CoV-2 antigens[12]. ELISA can identify previous infections, demonstrate immunity in vaccinated or infected individuals, and monitor the persistence of antibodies. Antibody tests are used in seroprevalence studies or multisystem inflammatory syndrome in children, a late-onset post-infectious complication.

Conversely, rapid point-of-care (POC) tests aim to confirm or rule out COVID-19 infection in people with or without COVID-19 symptoms. Most of the marketed POC tests utilize the detection of SARS-CoV-2 antigens or host antibodies[13] and are microfluidic test devices. The calorimetric signal result appears positive or negative in patients with IgG-type antibodies in <20 min. Point-of-care tests at the time of admission could be helpful in resource-limited countries where polymerase chain reaction (PCR) is not readily available[14].

In this study, we aimed to determine the diagnostic performance of two different ELISA techniques by comparing the IgG antibody levels between the POC and traditional ELISA techniques in individuals who have not contracted COVID-19 and have received the complete vaccination schedule.

Materials and Methods

Samples

Blood samples were obtained in a ethylenediamine tetraacetic acid-containing hemogram tube from all patients in August 2021. Informed consent was obtained from all patients prior to the blood draw. After obtaining the blood samples, the plasma was separated by centrifugation, and all samples were stored at -20 °C until use.

The samples were tested with POC IgG ELISA, and the results were compared with two different traditional ELISA kits [Euroimmune (PerkinElmer, Lubeck, Germany) and Genzbio Covel (Bilkent University, Ankara, Turkey) quantitative SARS-CoV-2 IgG ELISA] to determine the IgG antibody levels. All analyses were performed simultaneously on the same day and on the same sample. The World Health Organization's (WHO) SARS-CoV-2 IgG antibody reference serum sample was used in the study [level, 250 international units (IU)/ml].

Point-of-care ELISA: This technique detects the presence of IgG in the serum, plasma, or blood samples. Horseradish peroxidase converts specific indicators to a detectable colorimetric signal. Protein A was used in the POC ELISA device as the positive control for assessing the validity of the test. It took 20 minutes to perform the test. Manual application of the test reagents took 15 minutes, and reading the results with the Genz-Pro device took 5 minutes.

Euroimmune SARS-CoV-2 IgG ELISA: This test is based on enzyme immunoassay principles. The results were negative if the titers are <0.8, borderline if the titers were 0.8-1.1, and positive if the titers were ≥1.1. Multiplying these results with 3.2 provided the binding antibody unit with the WHO standard.

Genzbio SARS-CoV-2 IgG ELISA: This test is based on enzyme immunoassay principles. After obtaining the antibody titers, a standard logarithmic curve was created using the application, and the concentration was calculated. To ensure the correlation of the results obtained in relative units (RU/ml) with the WHO standard, the concentrations obtained were multiplied by 4.5 to obtain values in IUs.

Statistical Analysis

Statistical analysis was performed using IBM Statistical Package for the Social Sciences 20.0 (IBM Corp., Armonk, NY, USA). A p-value of <0.05 was considered statistically significant. Data are presented as mean and percentages. The Kolmogorov-Smirnov test was used to assess the normality of the distribution of the evaluated parameters. The Pearson chi-square test was used to analyze categorical variables. Spearman's correlation was used to analyze the association between numerical parameters.

Ethics Approval

The study was approved by the Ethics Committee of the Near East University (no: YDU/2021/93-1383, date: 29.07.2021).

Results

A total of 84 individuals who had not previously contracted COVID-19 were included in the study. Of the 84 individuals, 15 participants who had never been vaccinated formed the control group. Because it is difficult to find unvaccinated individual who had never contracted COVID-19, children aged >14 years were included in the control group. Thirty-one participants had received the Comirnaty vaccine and 38 had received the CoronaVac vaccine. Additionally, patients in whom at least one month had passed since their last vaccination were included in the study. The vaccine had been administered according to the COVID-19 guidelines of the Ministry of Health of the Republic of Turkey[3].

A total of 84 individuals were included in our study with 65 (85%) females and 35 (15%) males. The mean age of the individuals was 37±14 years (range, 1574). Fifteen individuals who had not been vaccinated against COVID-19 were included in the study as the control group. The mean age of the control group was 17.6 years. The demographics and vaccination status of the individuals are shown in Table 1.

The antibody results were also studied using Genz-Pro, a POC test that was used to assess the samples obtained simultaneously with ELISA. A sample picture of the results obtained is shown in Figure 1. Of the 38 individuals vaccinated with CoronaVac, 22 had positive Genz-Pro results. Of the 31 individuals vaccinated with Comirnaty, 30 had positive Genz-Pro results. The positive detection rate was significantly higher in Comirnaty-vaccinated patients than in CoronaVac-vaccinated patients, which was statistically significant according to the Pearson chi-square test (value=13.899; p<0.005)

Antibody results obtained using the two kits were evaluated based on gender and vaccination status (Table 2). The Spearman's

Table 1. Demographic data and vaccine status of the study participants

Characteristic	n (%)
Sample	84 (100)
Vaccinated group	69 (83)
Control group	15 (17)
Vaccinated group	
CoronaVac	38 (45)
Comirnaty	31 (37)
Sex, M/F	35 (15)/65 (85)
Age, years (mean±SD)	37±14

M/F: Male/female, SD: Standard deviation

Table 2. Comparison of the results between the Euroimmun and Genz Covel ELISA methods

Variable	Euroimmun ELISA, p value	Genz Covel ELISA, p value
Sex	0.747	0.807
Vaccine status		
No vaccine - CoronaVac	0.001	0.005
No vaccine - Comirnaty	0.0001	0.0001
CoronaVac - Comirnaty	0.0001	0.0001
Antibody titers, IU/ml		
Comirnaty, median (IQR)	325 (114-384)	76 (30.5-450)
CoronaVac, median (IQR)	81.2 (0-391795.6)	31.7 (0-161.7)

ELISA: Enzyme-linked immunosorbent assay, IQR: Interquartile range

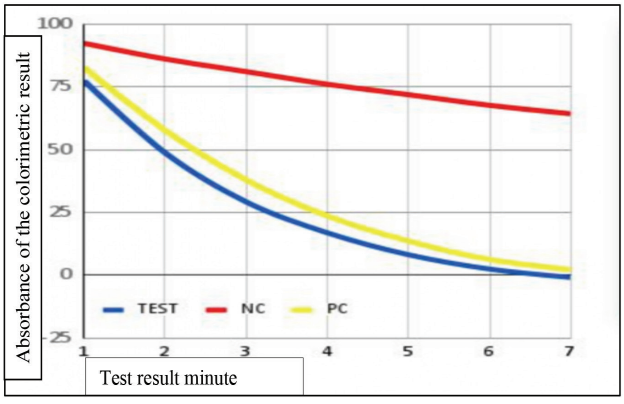

Figure 1. A sample Genz-Pro test result

Test: Patient result, NC: Negative control, PC: Positive control

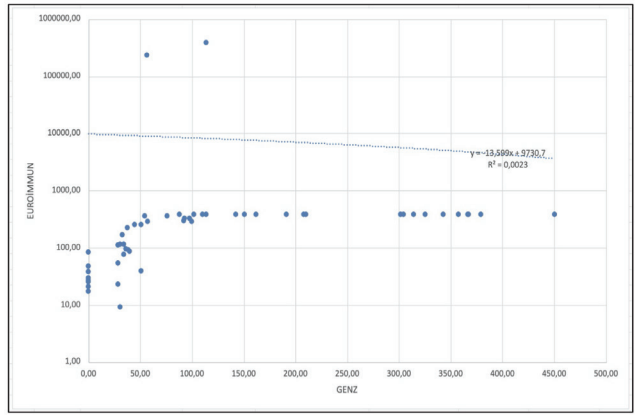

Figure 2. Spearman's correlation between the Euroimmun and Genz Covel ELISA methods

NC: Negative control, PC: Positive control, Ab: Antibody

correlation coefficient demonstrated a positive correlation between the results obtained (r=0.914; Figure 2). There was a correlation accumulation between both methods at 50 IU/ml.

The mean antibody titer of the patients was 7695.6 IU/ml and 149.6 IU/ml in the Euroimmun and Genz Coval ELISAs, respectively. A statistically significant difference was found in the antibody titers between the vaccine types (p=0.0001).

The patients were followed up for 6 months after the study period. Five people contracted PCR-confirmed COVID-19. These participants had been vaccinated with two doses of the CoronaVac vaccine and had developed the disease on an average of 4.4 months after receiving the vaccine.

Discussion

This study evaluated the diagnostic performance of two different ELISA techniques and one POC assay, and the IgG antibody titers were compared between two groups (patients vaccinated and not vaccinated with the COVID-19 vaccine). The advantages of the POC method are that it produces results faster and provides a curved result by obtaining multiple measurements without any end-point (Figure 1). The group vaccinated with Comirnaty showed 97% immunity. Point-of-care tests are being increasingly preferred because they are portable and cost-effective, the sample requires lesser processing, and the sample need not be transferred to the central laboratory[15]. Considering the recent increase in the number of daily cases, governments have to consider limiting the use of the PCR tests due to time-constraints and cost-effectiveness and to launch new screening tests. Our findings show that POC ELISAs may find a wide range of uses during and after the COVID-19 pandemic.

We also analyzed the antibody titers in individuals after COVID-19 vaccination with two traditional ELISAs. The Euroimmune and Genz Covel tests were used to quantitatively detect IgG-type antibodies against SARS-CoV-2. Both methods were positively correlated in our study, indicating that the antigens' diagnostic capacity is appropriate (Figure 2). Additionally, the significantly higher median antibody titer in individuals who had received the Comirnaty vaccine (Table 2) suggests that the immunity will be maintained for a more extended period after this vaccine. The Genz Covel test used specific recombinant SARS-CoV-2

antigens, and the Euroimmune test used modified nucleocapsid protein antigens. This difference in antigen may explain the different antibody titer measurements obtained in the two vaccine groups. There are several studies on Euroimmune testing across time series in patients with PCR-confirmed COVID-19[16-20]. However, studies on the use of ELISA tests to determine post-vaccine immunity are limited.

Our study investigated the seroconversion of IgG antibodies in the two vaccine groups and a control group. More seroconversions were detected in the Comirnaty vaccine group than in the CoronaVac vaccine and control groups. According to the WHO, as of December 28, 2021, there have been 137 clinical trials and 194 pre-clinical trials related to these vaccines[21]. Tanriover et al.[22] determined that the Sinovac vaccine was highly effective in preventing symptomatic COVID-19 (83.5% effective relative to the placebo). In our study, three patients immunized with the CoronaVac vaccine developed COVID-19 after an average of four months. This suggests the importance of booster doses and that the Comirnaty vaccine is more effective than the CoronaVac vaccine. Polack et al.[14] determined the effectiveness of the Comirnaty vaccine to be 95%.

The continuous emergence of vaccine-resistant mutations also reduces the effectiveness of vaccines. However, there has been a substantial drop in the neutralizing antibody titers against variants in those immunized with Comirnaty[23]. Neutralizing antibody titers are primarily used in studies to demonstrate the protection that develops with the vaccine. However, the difficulty of this test and the need for a biosafety cabinet are the most significant disadvantages. Traditional ELISA methods provide an idea regarding the protection level and can be used in seroprevalence studies.

Study Limitations

A limitation of our study was that the antibody titers could not be measured at certain times after vaccination. Observing antibody titer monitoring at regular intervals after vaccination will be more real data in predicting the protection of vaccines.

Conclusion

Our study findings demonstrate that the POC ELISA can quantify IgG seroconversion after COVID-19 vaccination with rapid and multiple measurements without sample accumulation. The POC ELISA can be used in COVID-19 services and outpatient clinics during post-vaccination follow-up to determine the performance of vaccines.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of the Near East University (no: YDU/2021/93-1383, date: 29.07.2021).

Informed Consent: Informed consent was obtained from all patients prior to the blood draw.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.S., Design: M.S., S.A., Data Collection or Processing: S.A., Analysis or Interpretation: M.S., S.A., Literature Search: E.K., Writing: M.T.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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