antispike dan vaksin

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ДИНАМИКА IgG-АНТИТЕЛ ПРОТИВ RBD УЧАСТКА S-БЕЛКА SARS-CoV-2 ПОСЛЕ ВВЕДЕНИЯ CoronaVac: ДЛИТЕЛЬНОЕ НАБЛЮДЕНИЕ

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Резюме. Сообщений о титрах антител после введения CoronaVac по-прежнему мало, особенно когда речь идет об эффективности CoronaVac после вакцинации среди населения Индонезии. Целью данного исследования является определение эффективности вакцинации против COVID-19 путем сравнения уровней IgG против S1 субъединицы RBD SARS-CoV-2 после первой и второй вакцинации. Исследователи собрали образцы венозной крови у участников после того, как они получили вакцину CoronaVac 600 SU/0,5 мл с двумя разными интервалами (14 дней и 28 дней). Кровь брали дважды (после первой и второй вакцинации) и тестировали на антитела (значение положительного обнаружения антител 50 AU/мл). Парные данные были проанализированы с использованием критерия Уилкоксона (числового) или критерия Макнемара (категориального). Средние уровни IgG1 в 14-дневном интервале между дозами вакцины составляли 64,40 AU/мл, а уровни IgG2 составляли 886,10 AU/мл. При этом средний уровень IgG1 составил 146,10, а уровень IgG2 – 688,00 AU/мл в группе с 28-дневным интервалом между дозами вакцины. После первой вакцинации 60,00% обследованные имели положительный уровень IgG, который увеличился до 98,57% после второй вакцинации. После вакцинации полной дозой все участники имели достоверно более высокие уровни антител. Эффект был сильнее в группе, получавшей вакцину с 14-дневным интервалом. Также было показано, что CoronaVac увеличивает встречаемость антител у участников исследования.

Ключевые слова: антитело, условная единица, CoronaVac, рецептор-связывающий домен, SARS-CoV-2

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ANTI-SARS-CoV-2 SPIKE RECEPTOR BINDING DOMAIN (S-RBD) IgG ANTIBODIES FOLLOWING CoronaVac ADMINISTRATION: A LONGITUDINAL STUDY. ANTI-SARS-CoV-2 S-RBD IgG ANTIBODIES

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Abstract. Reports on antibody titers following CoronaVac administration are still scarce, particularly when it comes to the post-vaccination effectiveness of CoronaVac in the Indonesian population. The purpose of this study is to determine the efficacy of COVID-19 vaccination by comparing the IgG levels against the S1 subunit of SARS-CoV-2 RBD after the first and second vaccinations. The researchers collected venous blood samples from participants after they received the CoronaVac 600 SU/0.5 mL vaccine at two different intervals (14 days and 28 days). Blood was drawn twice (after the first and second vaccinations) and tested for antibodies (positive antibody detection value of 50 AU/mL). Paired data were analyzed by using either the Wilcoxon test (numerical) or the McNemar test (categorical). The median IgG1 levels in the 14-day interval between vaccine doses were 64.40 AU/mL and IgG2 levels were 886.10 AU/mL. Meanwhile, the median IgG1 level was 146.10, and IgG2 level was 688.00.AU/mL in the group with a 28-day interval between vaccine doses. After the first vaccination, 60.00 % of study subjects had positive IgG levels, which increased to 98.57% after the second vaccination. Following the full-dose vaccination, all participants had higher antibody levels, and considered significant. The effect was stronger in the group that received the vaccine at 14-day intervals. CoronaVac has also been shown to increase the prevalence of detectable antibody positivity in study participants.

Keywords: antibody, arbitrary unit (AU), CoronaVac, receptor binding domain, SARS-CoV-2

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Introduction

The SARS-CoV-2 infection has emerged as an issue globally with its serious pathogenicity and contagious potential. It is based on the presence of virus transmission from asymptomatic and presymptomatic individuals. Hence, various efforts are made to control and prevent infection, including vaccination. The development of a vaccine is implemented quickly which aims to avoid infection and prevent symptoms of COVID-19, thus reducing harmful consequences [18].

The main strategy employed in various COVID-19 vaccine candidates is to create vaccines capable of inducing antibodies against the receptor-binding domain (RBD) [13]. As widely known, SARS-CoV-2 has a spike protein (S) on its surface. The viral S protein will attach to its receptor on the host surface of the cell, Angiotensin-Converting Enzyme 2 (ACE-2). This attachment process depends on a domain of the S protein known as the RBD. The main immune pathway for preventing infection is to restrict viral binding to ACE-2 [18].

Some vaccines have been developed rapidly, with varying mechanisms of action. These include nucleic acid (RNA and DNA) vaccines, viral vector (replicating or non-replicating) vaccines, inactivated viral vaccines, protein subunit vaccines, virus-like particle vaccines, live attenuated vaccines, lentiviral vector-modified artificial antigen-presenting cells (APCs), and dendritic cell vaccines [5, 10, 17]. The non-replicating viral vector-based (24%) and RNA-based (20%) vaccines are two of the most widely developed vaccine forms [17]. Some vaccines have received emergency use authorization (EUA), an approval that allows them to be used in the general population [9].

Since early 2021, governments in several countries, including Indonesia, have launched a COVID-19 vaccination campaign to combat the disease's spread. COVID-19 vaccines of various types, including mRNA and inactivated vaccines, are used. However, reports on post-vaccination antibody levels need to be expanded. This is due to the wide variability of immune responses to SARS-CoV-2 following the vaccination [14].

The inactivated vaccine (CoronaVac) manufactured by Sinovac is the most commonly used SARS-CoV-2 vaccine in Indonesia [15]. This vaccine is administered intramuscularly in two doses of 0.5 mL each. The interval between each dose is four weeks [21]. From early November 2021, this vaccine is approved for children aged 6 to 11 years [4].

The immune response to vaccines is influenced by a variety of factors, including vaccination program quality (type of vaccine, age of recipients, the interval between doses, vaccine potency, formulation and stability, vaccine administration and vaccination schedule), host-related factors (age, gender, genetic factors, smoking, and nutrition), and environmental factors [6]. One method for determining the immune response to vaccines is to evaluate the level of antibodies formed after vaccination. Antibodies produced as a result of vaccination can be IgM at first, then IgG, and finally IgA. IgG is known to have good affinity and neutrality against antigens among these antibody classes, making it reliable for detecting immune response and vaccine effectiveness following COVID-19 vaccination [12].

Reports on antibody titers following CoronaVac administration are still scarce, particularly when it comes to the post-vaccination effectiveness of CoronaVac in the Indonesian population [20]. The efficacy of COVID-19 vaccination, particularly the inactivated vaccine type, is still being studied, particularly in terms of a sufficient antibody titer threshold to stimulate a protective effect. The purpose of this study is to determine the efficacy of COVID-19 vaccination by comparing the IgG levels against the s1 subunit of SARS-CoV-2 RBD after the first and second vaccinations.

Materials and methods

Study overview

We collected data in two instances: through questionnaires and blood testing. The questionnaire includes sociodemographic information and history of confirmed COVID-19 cases (for exclusion of participants who have been contracted with COVID-19). Venous blood samples were obtained to determine post-vaccination immunoglobulin G (IgG) levels after receiving CoronaVac 600 SU/0.5 mL (Sinovac Life Sciences, Beijing, China) with two different dosing interval (14 days and 28 days). Sample collection was done between March to June 2021. This study was approved by the Institutional Review Board of Faculty of Medicine, Universitas Sriwijaya (approval number: 062-2021).

Blood collection and antibody examination

The blood sampling steps were repeated twice, with 3 cc of blood obtained (from the median cubital vein) for each sample collection (13-14 days after the first dose of vaccination and 30±2 days after the second dose of vaccination). Blood samples were placed in non-anticoagulant tubes to obtain the serum to be examined.

IgG concentrations were assessed utilizing Abbott SARS-CoV-2 IgG II Quant assay (from 75 μL of serum sample). The Architect TM i2000 analyzer (Abbott) then analyzed it using the Chemiluminescent Microparticle Immunoassay (CMIA) method. When the antibody titer level reached 50 arbitrary units per milliliter (AU/mL), the result was considered reactive. Meanwhile, a value of < 50 AU/mL is defined as non-reactive [2]. Calibration was performed before each test. The IgG evaluation for SARS-CoV-2 RBS subunit s1 was performed in the Clinical Pathology Laboratory of Mohammad Hoesin Hospital.

Statistical analysis

The data was analyzed using the IBM SPSS Statistics for Windows, Version 24.0 program (Armonk, NY: IBM Corp.). The characteristics of the research subjects were displayed in the form of a frequency distribution table, including the concentration and dispersion calculations (maximum, minimum, mean, median, and standard deviation values). Differences in first and second IgG levels were analyzed using the paired T-test for data with a normal distribution or the Wilcoxon test for data with an abnormal distribution (numerical variable). Meanwhile, for the categorical variable, McNemar test was conducted. The threshold of significance was set at $p < 0.05$.

Results

This study included 70 people who had received a complete COVID-19 vaccination (2 doses) with the CoronaVac vaccine. Health workers, public-sector employees, and the elderly were among the research participants. Table 1 displays demographic information about the participants.

Table 1 shows that the majority of the participants were between the ages of 26 to 45. The subjects in the study ranged in age from 20 to 68 years old, with an average age of 35.63 years (median: 35 years). The number of male and female participants was almost equitably spread. In terms of vaccine intervals, the majority of study subjects (61.43%) had vaccine intervals of 28 days.

TABLE 1. SUBJECT CHARACTERISTICS

Variabel	Median ± IQR	Mean ± SD	n	%
Age (years) **Age (14-days interval)** **Age (28-days interval)**	35.00±23.00 21.00±1.00 42.00±21.00	35.63±13.91 23.07±5.34 43.51±11.63		
Age group (years) 18-25 26-45 46-65 ≥ 65			 25 29 14 2	 35.71 41.43 20.00 2.86
Gender				
Male	–	–	33	47.14
Female	–	–	37	52.86
First and second vaccination interval				
14 days	–	–	27	38.57
28 days	–	–	43	61.43

Note. IQR, Interquartile range; SD, Standard deviation.

TABLE 2. ANTIBODY RESPONSE ASSESSMENT

Variable	After 1st dose	After 2nd dose
Positive (%) **Negative (%)**	42 (60.00%) 28 (40.00%)	69 (98.57%) 1 (1.43%)
Elevated antibody (%)	70 (100.00%)	

TABLE 3. ANTIBODY LEVELS FOLLOWING THE VACCINATION WITH CoronaVac

Variable	After 1st dose	After 2nd dose	p value
Serum sample			
Antibody (+) 28 days interval 14 days interval	 28 (65.1%) 14 (51.9%)	 42 (97.7%) 27 (100.0%)	1.000[a]
Antibody level			
28 days interval	146.10±845.00 AU/mL	688.00±1157.80 AU/mL	0.036 [b]
14 days interval	64.40±759.90 AU/mL	886.100±683.40 AU/mL	< 0.001 [b]
Total	88.60±759.90 AU/mL	766.15±968.32 AU/mL	< 0.001[b]

Note. Data were presented Median ± Interquartile Range (IQR). Statistical analysis was done using the (a) McNemar and (b) Wilxocon test, $p < 0.05$.

We observed the clinical effect of CoronaVac vaccination on participant antibody formation. All participants had elevated antibody counts from the first to the second vaccination, with only one subject (1.43%) having undetectable antibody levels despite being fully vaccinated. Table 2 contains the specifics. Table 2 contains the specific details.

Regarding the clinical implication, we examined the vaccine's efficacy based on dosing intervals (14-days or 28-days). Following the full dose, we discovered that both types of vaccines were able to raise antibody levels, resulting in a positively-detected quantity of antibodies (≥ 50 AU/mL). We also discovered that the elevation of antibody amount between the first and second doses was significant in both dosing, but it appears to be more significant in the group that received the full dose within 14 days of the interval ($p < 0.001$ *vs* $p = 0.036$). The same result was obtained when the analysis was performed without regard for the respective dosing interval group ($p < 0.001$). Table 3 contains more information on these findings.

Discussion

COVID-19 vaccination using various vaccine types has been implemented globally to counter the effects of the pandemic. Vaccination is effective in preventing serious disease manifestation, hospitalization, and mortality [1, 7]. This study included 70 people who had received a full COVID-19 vaccination (2 doses) with the CoronaVac vaccine, with either a 14-day or a 28-day dosing interval.

According to the findings of this study, approximately 60% of the participants had positive IgG levels after the first vaccination, whilst almost all of the participants had positive IgG amounts after the second vaccination. These findings are similar to those of Binay et al. who found that 100% of participants had positive IgG levels after receiving two doses of the CoronaVac vaccine [3]. Meanwhile, Bayram et al. found that after CoronaVac vaccination, IgG was found to be positive in 77.8% of participants after the first vaccination and 99.6% of subjects after the second vaccination [2].

The IgG assessment after the first and second vaccinations was found to be highly variable in this study, and mainly explained as the effect of heterogenous individual immune response [11]. The median IgG1 (first dose) level was 64.40 AU/mL and the IgG2 (second dose) level was 886.10 AU/mL in the 14-day dosing interval. Meanwhile, the median IgG1 level for the group with a 28-day dosing interval was 146.10 AU/mL, and the IgG2 level was 688.00 AU/mL. Conversely, in phase 1/2 trials conducted by Zhang et al. with participants aged 18-59 years, they discovered that subjects who had a 28-day interval between CoronaVac vaccine doses had higher antibody levels than those with a 14-day interval [22]. However, a Turkish study found that vaccine effectiveness (as measured by seroconversion rates) did not differ significantly between vaccine schedules (14-day or 28-day intervals) [19].

The differences identified in this research may be explained by the age differences between the study subjects in both interval groups. The 14-day vaccine interval group was significantly younger than the 28-day vaccine interval group (median: 21.00 years *vs* 42.00 years). Previous research on the use of the CoronaVac vaccine has described this age-related phenomenon, with older age being associated with lesser immune response, lower maximum antibody levels, and faster antibody decline [16]. Other potential reasons for this finding are related to immunodominance. Immunodominance is an immunological condition in which immune responses are directed against only a subset of the antigenic peptides formed. Previous research has discovered at least six immunodominant epitopes that differ from the previously identified immune response (reflected as specific antibodies production) and can alter vaccination efficacy [8]. However, no specific explanation regarding the influence of age (mean or median value) and vaccination interval which has been described in previous study [22].

Our study had a higher median SARS-CoV-2 anti-spike IgG2 value (following two CoronaVac 766.15 AU/mL *vs* 547.7 AU/mL) than Keskin et al. (766.15 AU/mL *vs* 547.7 AU/mL). However, no specific dosing intervals were mentioned in the comparison study [8]. Meanwhile, we measured the IgG2 level one month after the second dose of vaccination. Some important factors causing these differences (as observed in several studies) include the length of follow-up and country-level experience with inactivated virus vaccines [21].

Our research has several limitations. Mainly, it is related to the small sample size used in this study. Then, due to the government vaccination regulation of CoronaVac, which follows a 4 week (28 day) interval between vaccine doses, no additional participants with a 14-day interval can be included. Our analyses were affected by the absence of more refined covariates such as chronic illness (comorbidities) which could influence vaccine effectiveness.

Conclusion

CoronaVac administration at both dosing intervals (14-days and 28-days) is effective in enhancing antibody levels ($p < 0.05$). The effect appears to be prominent in the 14-day dosing interval group. Our study also discovered that 60.00% of participants have positive IgG levels (≥50 AU/mL) after the first vaccine dose, and this number rises to 98.57% after

the second vaccination. Future studies with larger samples and correlating the results with genetic factors of participants due to interpersonal immune variability can be proposed. Further comparison with similar research, particularly in the Indonesian population, is required for improved overall validity. In addition, due to contradictory results with the established protocols (longer interval gives a better level of detected antibody), it is suggested to assess total antibody and antibody against different inductors (such as protein N) in forthcoming studies.

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