International Journal of Public Health Science (IJPHS)
Vol. 13, No. 2, June 2024, pp. 775~782
ISSN: 2252-8806, DOI: 10.11591/ijphs.v13i2.23701

Adverse events following immunization of mRNA-1273 (Moderna) booster vaccine in clerkship students

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Article Info

Article history:

Received Aug 1, 2023
Revised Oct 19, 2023
Accepted Oct 28, 2023

Keywords:

AEFI
Booster vaccine
Clinical clerkship students
COVID-19
mRNA-1273 (Moderna)

ABSTRACT

Two-dose primary vaccine administration was the best strategy to reduce the prevalence and severity of COVID-19. Improved immunity and antibody response to the new variant virus by administering a booster vaccine is needed. Health workers are the main priority for administering the mRNA-1273 (Moderna) booster vaccination in Indonesia. This vaccine has high effectiveness, and safety, however, data and evaluation of adverse events following immunization (AEFI) is required. This study aimed to determine the AEFIs of mRNA-1273 booster vaccination in clinical clerkship students as an early adult age group. The research design was a repeated cross-sectional study using purposive sampling technique. There were 214 subjects who met the requirements. Subject filled out an online questionnaire containing evaluation of AEFIs. The most local AEFIs symptoms were pain at the injection site (79.0%), while the common systemic symptoms were headache, drowsiness, weakness, and fever (37.4%; 26.2%; 9.8%; 9.3%). Most AEFIs were felt within 30 minutes to three days. No respondents required hospitalization, experienced anaphylactic shock, became disabled, or died. The AEFIs did not have a significant relationship with gender, history of allergies, co-morbidities, or history of COVID-19. This information is used as a preventive or educational effort to support implementation vaccine in Indonesia.

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1. INTRODUCTION

On Friday May 5, 2023, World Health Organization (WHO) officially ended the COVID-19 "global health emergency" status [1]. However, on May 8, 2023 there were still 1,149 positive cases and 21 deaths of COVID-19 in Indonesia [2]. The current incidence of COVID-19 in Indonesia has decreased compared to the beginning of the pandemic on March 11, 2020 [3]. The Indonesian government implemented several prevention strategies in the early stages of the pandemic to suppress the spread of COVID-19, including wearing masks, maintaining social distancing, avoiding crowds, and limiting unnecessary travel. However, restrictions on people's daily activities added to the economic burden and not a long-term solution. Vaccine development has proven to be the best strategy for reducing the prevalence and severity of the disease [4]. In a short time, vaccine technology developed, such as through techniques using nucleotide acids (DNA and RNA), viral vectors, inactivated and protein-based vaccines. During the pandemic there were 33 vaccines that were used by countries around the world [5]. Even though vaccination has the effect of controlling the

pandemic, we need to be wary of the emergence of new variants whose spread and effects cannot be predicted. Hence, the effectiveness and safety of existing vaccines needs to be evaluated and developed in the future. Health workers are at risk of transmitting COVID-19, therefore they deserve special attention to get protection regarding the long-term safety of the vaccine and its side effects.

The effectiveness of the two-dose primary COVID-19 vaccination significantly reduces hospitalizations and high infection rates. Studies showed high effectiveness BNT162b2 (Tozinameran/Pfizer-BioNTech) and mRNA-1273 (Elasomeran/Moderna) after six month vaccination, against severe disease, hospitalization, and death [6]. Effectiveness against symptomatic SARS-CoV-2 infection in the general population ranged from 89-97% for BNT162b2 (Pfizer-BioNTech), 92% for ChAdOx1 nCoV-19 (Oxford-AstraZeneca), and 94% for mRNA-1273 (Moderna) [7]. BNT162b2 and mRNA-1273 are mRNA vaccine, encoding the SARS-CoV-2 spike protein which provide a strong amplifying effect with low reactogenicity. Modified bivalent booster vaccine containing mRNA which encoding the spike protein of the beta and ancestral variant of SARS-CoV-2, produces a superior and long-lasting neutralizing antibody response against the beta, delta, and omicron variants [8]. Moreover, booster vaccination is the best model increasing immunity and strengthening antibody responses against new virus variants in the future [9].

Several countries have started offered booster doses of COVID-19 vaccines for high-risk groups and for the adult population [7]. The Indonesian government also required all primary vaccines and booster to reduce the incidence of COVID-19. Therefore, the Ministry of Health of the Republic of Indonesia issued a circular regarding the administration of booster vaccines to all health workers, health assistants, and supporting staff in health care facilities in July 2021 [10]. The type of booster vaccine of COVID-19 for health workers in Indonesia is the mRNA-1273 (Moderna) vaccine [11]–[13]. Recommended booster dose is half the dose (50 µg) of mRNA-1273 (Moderna), no earlier than six months after the primary vaccine (doses 1 and 2) completed [6]. Several studies have confirmed the safety of the mRNA-1273 vaccine, which serves as primary and secondary (booster) [13], [14]. Although, after the primary and booster of COVID-19 vaccination, people can experience adverse events following immunization (AEFI). AEFIs is any unwanted medical events that occur after immunization and do not necessarily have a causal relationship with the use of vaccines [12]. AEFIs is one of the factors related to public perception of vaccine safety, thus the community's decision to accept or reject vaccines.

The main target of the booster vaccination mainly are the health workers, elderly and vulnerable groups. The clerkship students are categorized as the early adult age group of health workers who recommend to receive the vaccine booster [15]. The data or information about AEFIs in Indonesia especially after administration of the mRNA-1273 vaccine booster including in early adult age group are limited. Some factors might contribute to the AEFIs, for example gender, the history of COVID-19, the history of allergy, and having comorbid disease. However, the previous study in Indonesia only mentioned about the percentage of nursing student who had AEFIs [16], while other study considered gender as the related factor. There is one study in Indonesia had clerkship student as subjects, but the type of vaccine and variables to be analyzed was different [17]. The fear of the AEFIs might cause reluctance among the early adult age group meanwhile they can be the virus carrier to their family due to their activities. The evidence-based related to AEFIs is crucial for policy maker, vaccine developers, and community including health workers. Obtaining AEFIs of mRNA-1273 data would give information of the benefits and risks of vaccines, supporting alternative vaccination strategies, and considering strategies to maximize the level of AEFI protection. Therefore, the study aim is to investigate the AEFIs of booster doses of vaccines in clinical clerkship students as health workers and an early adult age.

2. METHOD

This research is a repeated cross-sectional study conducted at Syarif Hidayatullah State Islamic University Jakarta from August 31-September 2, 2021. The population for this study was clinical clerkship students at Syarif Hidayatullah State Islamic University Jakarta that received priority from the South Tangerang health office to get a booster vaccine. The inclusion criteria were all clinical clerkship students who received the mRNA-1273 (Moderna) booster vaccine 0.5 ug (0.25 ml) intramuscularly [9], and willing to participate by filling out a complete questionnaire immediately after receiving vaccine booster until seven days after vaccination. Subjects with a history of COVID-19 less than three months, history of allergy to the COVID-19 vaccine, blood clotting disorders, autoimmune disorders, administration of other vaccines under 14 days and failure to provide informed consent were excluded from this study. The sampling technique was carried out by purposive sampling and 214 subjects met the requirements to participate in this study.

The questionnaire was developed based on the AEFIs standard set by the Ministry of Health of Indonesia included basic characteristics of subject, allergy history, comorbidities, history of COVID-19 infection more than three months and complete AEFIs symptoms. AEFIs symptoms was distinguished as

localized and systemic symptoms, which can occur quickly or slowly [14]. After received the mRNA-1273 booster vaccine, the subjects were asked to fill in the online questionnaire. This research uses a standard questionnaire for measuring AEFIs and some modification which has been tested for validity and reliability. Based on to the value of Cronbach's alpha 0.75, the questionnaire was valid and reliable. The questionnaire was sent to the subject four times to evaluate the AEFI, they might have at 30 minutes, 24 hours, three day, and seven days after they received the booster vaccine [18], [19]. The descriptive and statistically analysis was performed using Microsoft Excel 2019 and SPSS 23.0. Gender characteristics and events of the AEFIs and its association were compared using the chi-square test. The statistical comparisons were performed using a predetermined significance threshold ($p<0.05$).

The study protocol was accepted by the Ethics Committee of the Faculty of Medicine Syarif Hidayatullah State Islamic University Jakarta, Indonesia, with registry number B 027/F12/KEPK/TL.00/04/2022. All methods were carried out in accordance with relevant guidelines and regulations in the Declaration of Helsinki. Informed consent was conducted from each subject before completing the questionnaire. All data obtained and used in this study will be kept confidential.

3. RESULTS AND DISCUSSION

3.1. Characteristics of subject

The characteristics of 214 clerkship students as the subjects of this study can be seen in Table 1. The mean of the age was 22.84 years, and the median was 23 years. The characteristics of these subjects are similar with the previous study related to AEFIs of the mRNA-1273 booster vaccine on health workers at Universitas Indonesia Hospital, Indonesia which consisted of 77.8% female and 22.2% male, while 31.5% were age <25. There were 10.5% had comorbidities, 19% had history of food allergy, 19 % had history of drug allergy, and 21.4% had history of COVID-19 [19]. Meanwhile another study in USA showed 89.35% were females and the remaining were males among mRNA-1273 vaccine recipients, with 6.02% belong to the age group between 18-30 years and the mean of the age was 43.76 years [20]. Other study in Indonesia among healthworkers, conducted by Pakki *et al.* showed different results such as female were 67.3%, and male were 33.7%, while 28.7% had history of COVID-19 and 10.9 had comorbidities [12].

Table 1. Characteristics of subject

Characteristics	Description	N (%)
Gender	Male	54 (25.2)
	Female	160 (74.8)
Allergy history	No	144 (67.3)
	Food	23(10.7)
	Drug	6 (2.8)
	Others	41 (19.2)
Comorbid disease	No	198 (92.5)
	Asthma	12 (5.6)
	Diabetes mellitus	0 (0)
	Psychosomatic disorder	2 (0.01)
	Hypertension	1 (0.005)
	COPD	1 (0.005)
COVID-19 history	Yes	48 (22.4)
	No	166 (77.6)

3.2. AEFIs with local symptoms

The localized and systemic symptoms at 30 minutes, 24 hours, 30 days, and seven days, were assessed by the respondent and reported in Tables 2 and 3. For the localized symptoms, during monitoring for the first 30 minutes after the booster vaccination, 37.9% experienced pain at the site injection, while 52.3% of students were asymptomatic, as shown in Table 2. In the next 24 hours, the number of pain complaints at the injection area increased to 79.0%, but between three and seven days, only 17.8% subjects had symptoms, and only 2.8% still complained on the 7th day. Soreness at the injection site was felt by 9.3% in the first 30 minutes, 17.3% subjects in 24 to 72 hours and only 1.4% still had the complaint at 7th day. Participants had a burning sensation at the injection site mostly in 24 hours (1.4%), while 1.4% of participants complained of redness, and 2.3% complained of swelling between 3-7 days after vaccination.

Table 2. AEFI with local symptoms

Side effects Local symptoms	30 minutes	24 hours	24-72 hours	3-7 days	7th days
No symptoms	52.3%	3.7%	12.1%	70.1%	95.3%
Pain at the injection site	37.9%	79.0%	70.6%	17.8%	2.8%
Redness at the injection site	0%	0%	0%	1.4%	0%
Swelling at the injection site	0%	0%	0%	2.3%	0%
Burning sensation at the injection site	0.5%	1.4%	0%	0.9%	0.5%
Soreness at the injection site	9.3%	15.9%	17.3%	7.5%	1.4%

Table 3. AEFI with systemic synptoms

Side effects Systemic symptoms	30 minutes	24 hours	24-72 hours	3-7 days	7th days
No symptoms	77.6%	14.5%	22.4%	74.8%	94.9%
Headache	6.5%	31.8%	37.4%	12.1%	3.3%
Drowsiness	12.1%	26.2%	15.0%	6.5%	0.9%
Weakness	2.3%	9.8%	9.3%	2.3%	0%
Fever	0.5%	7.0%	9.3%	0.9%	0%
Fatigue	0.5%	2.3%	1.4%	2.3%	0%
Insomnia	0.5%	6.5%	3.3%	0.5%	0.9%
Nausea	0%	0.5%	0.9%	0.5%	0%
Chills	0%	1.4%	0.4%	0%	0%
Anaphylactic shock	0%	0%	0%	0%	0%

3.3. AEFIs with systemic symptoms

Table 3 shows that 31.8% of students complained of headache in the first 24 hours and increased to 37.4% between 24-72 hours. However, headache symptoms decreased to 12.1% between 3-7 days, and only 3.3% still had symptoms on the seven days. In the first 30 minutes, 77.6% of the participants had no systemic symptoms, but only 14.5% had no symptoms in 24 hours, thus 74.8% already had no symptoms after 3-7 days, and finally, 94.9% had no systemic symptoms on the day 7th. The results revealed that 12.1% experienced drowsiness in the first 30 minutes, which then increased to 26.2% after 24 hours, but decreased again by 6.5% between 3-7 days, and only 0.9% still complained on the seven days. Weakness was felt in the first 24 hours by 9.8%, but it dropped to 2.3%, between 3-7 days, and none of the participants complained on the seven days. The 7% of participants had fever in the 24 hours, which increase to 9.3% between 24-72 hours, before decreasing to 0.9 % after 3-7 days. Other symptoms such as fatigue only occurred 2.3% at 24 hours and 3-7 days, insomnia happened 6.5% at 24 hours and 3.3% between 24-72 hours, while chills occurred 1.4% at 24 hours and nausea symptom occurred 0.9% in 24-72 hours. The most common systemic symptoms were headache, drowsiness, weakness, and fever, as shown in Table 3. All local AEFI were mild, and none required hospitalization. None of them experienced shock postvaccination anaphylaxis, disability or death. Table 4 shows that the systemic AEFI had no significant association with gender, history of allergies, comorbid diseases and history of COVID-19 (all p-value>0.05).

Table 4. Association between gender, history of allergy, comorbid disease, history of COVID-19 and AEFI

Variable	AEFIs						p-value
	Yes		No		Total		
	n	%	n	%	N	%	
Gender							
Females	155	96.8	5	3.2	160	100	0.527
Males	53	98	1	2	54	100	
History of allergy							
Yes	69	98.5	1	1.5	70	100	0.361
No	139	96.5	5	3.5	144	100	
Comorbid disease							
Yes	15	93.7	1	6.3	16	100	0.376
No	193	97.4	5	2.6	198	100	
History of COVID-19							
Yes	48	100	0	0	48	100	0.213
No	160	96.3	6	3.7	166	100	

Health workers are at the forefront of fighting the ravages of COVID-19, hence, they are at greater risk of infection. The Delta variant from India dominated infection cases since the end of May 2021. This new variant is highly contagious, as evidenced the sudden increase in positive cases in Indonesia. Two doses

of Sinovac, which were administered to Indonesian health workers in February 2021, do not have a full protective effect. Most of them were still infected due to exposure to high doses of the virus in healthcare facilities, such as hospitals or health centres, and some deaths were also recorded. According to the WHO, mortality rate of COVID-19 ranges from 2 to 3% [3]. A previous study showed that two doses of the vaccine did not provide an adequate response in some people, hence, a third dose is needed to boost their immunity [21], [22]. The CDC also recommended the administration of a third dose, such as Pfizer BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) to protect them [14]. Due to the high percentage of health workers exposed to COVID-19, the Ministry of Health started a third dose vaccination program using the mRNA-1273 (Moderna) vaccine on July 16, 2021 [10].

Adverse events following immunization (AEFI) could happen after the primary or secondary (booster) of COVID-19 vaccination. AEFIs classification is divided into reactions related to vaccine components, vaccine quality defects, procedural errors, anxiety due to fear of being injected, and coincidental. Based on symptoms, the AEFIs is divided into mild and severe symptoms or serious and non-serious symptoms. Mild symptoms often occur in approximately 10% of patients, while severe AEFI is extremely rare [18], [23]. The AEFI of this vaccine includes "Moderna Arm", which can appear as a localized erythematous rash within a few days after the first dose. Most of the adverse effects are resolved spontaneously, but topical steroids and oral histamine have shown potency in relieving the rash and controlling symptoms [24]. Studies have reported that myocarditis is a rare severe systemic complication [25]. The management of mild AEFI is in accordance with the usual symptoms, while severe AEFI requires medical information.

Although the WHO stated that the benefits of using the vaccine outweigh the risks and potential for the AEFI, a lack of local information about the AEFI has a negative impact on people's perception of vaccine safety, which often leads to doubts. Recommending vaccination to family, friends, and the environment has an indirect effect to increase national vaccination coverage [26], [27]. Information on the incidence of AEFI affects participation and the level of public confidence in the benefits of the process [26]. The most common local adverse effects include pain at the injection site, which could occur after the first dose and second dose of vaccines. Other symptoms, such as headache, fatigue, fever, chills, joint pain, and nausea, are usually minor symptoms [20]. Studies also reported that reactogenicity was substantially greater after the second dose of vaccine, especially systemic reactions [28].

Our study showed that from 214 subjects, the most local adverse event after the third dose of mRNA-1273 vaccination was pain at the injection site. Only 2.3% complained of swelling between 3-7 days, like ‘Moderna Arms’. This study also showed systemic adverse events were headache, drowsiness, weakness, and fever. Headache was the most common systemic symptoms in this study. This result is similar with Menni *et al.* that reported adverse reactions after booster doses were similar to those after the second dose [7]. There is no severe systemic adverse event such as myocarditis or anaphylactic shock from our study while, there are small number of cases of myocarditis and/or pericarditis following mRNA vaccine (Pfizer-BioNTech/Comirnaty and Moderna/Spikevax with COVID-19 have been reported in Canada, Israel, United States (U.S.) and Europe, eventhough it resolved with symptomatic therapy within days [29].

Vaccines activate pattern-recognition receptors (PRRs), which promote the production of mast cells and macrophages, and release proinflammatory cytokines and vasodilators, which cause redness and swelling. Furthermore, neutrophils stick to the walls of the injured blood vessels and sensitize peripheral nociception by releasing cytokines, prostaglandins, or adenosine triphosphate (ATP), which interact with nociceptors (sensory neurons), causing pain in the injection area. These components may enter the bloodstream and produce other systemic factors, hence causing systemic symptoms such as headache, fever, myalgia, or rash [30]. A study by Einstein *et al.* suggested that headaches occur because the mRNA vaccine produces spike proteins that can cross the blood–brain barrier, causing intracranial inflammation [31].

AEFI is influenced by age and gender, but people with a history of allergies, comorbid diseases, and those with a history of COVID-19 infection may also experience an AEFI reaction after being vaccinated. According to Hidayat *et al.* age <25 years was found to have a significant effect on the AEFI [19]. This finding is in line with another study stated that the AEFI, was higher in the younger age group than at the elderly age group [13], [32]. However, the significant relationship between age and systemic AEFI of mRNA-1273 booster vaccination was not assessed in this research. This is because the participants were university students, with similar ages ranging from 20 to 26 years old, making it difficult to assess the association between age and AEFI. The relationship between gender and AEFI is another contributing factor. Although many studies have shown that the AEFI is higher in female students than in male students. The result shows no significant relationship between gender and the AEFI, as indicated in Table 4. It might be because the number of female respondents is higher than males (74.8% vs 25.2%). This study result is similar with the previous study by Pakki *et al.* among health workers that 45.6% subjects were <35 years, which also indicated gender has no relationship with AEFI [12].

A study by Hidayat *et al.* found that there was a significant relationship between the appearance of AEFI symptoms and a previous history of allergies [19]. Kadali *et al.* also found a relationship between a history of COVID-19 infection and the AEFI in the mRNA-1273 vaccine [20]. However, our research showed no relationship between history of allergies or history of COVID-19 infection and AEFI, as shown in Table 4. In our study, we have limited number of students with a history of allergies or a history of COVID-19 infection. It might be the reason for no significant relationship found with these variables. This study result is inline with the previous study by Tamin *et al.* which found that the history of COVID-19 infection had no relationship with the AEFI among health workers [33].

Based on current information that some of the main comorbidities are known to have an impact on AEFI, especially cardiovascular disease (CVD) and diabetes [30], [31]. However, in our study none of these three comorbidities were found, possibly because the subjects in this study were all groups of early adult or students aged between 20 to 26 years. Meanwhile, the other comorbidities are found in our study, namely hypertension, asthma, and COPD. However, no significant relationship was found with AEFI that occurred, because the number of students suffering from hypertension and chronic obstructive pulmonary disease (COPD) was only one subject for each comorbidity. Similar findings were also obtained in another study in Indonesia, in which both comorbid and no comorbid patients had the same risk of developing AEFIs [34].

The AEFI will be frequently encountered as part of the government's program to pursue mass COVID-19 vaccinations [35]. The WHO recommended the administration of the third dose vaccine to prevent exposure to COVID-19 and increase immunity of the community, including in people with a history of mild allergies and comorbidities. Moreover, the side effects of this vaccination are the community's concern and questions regarding the safety of the COVID-19 vaccine. Therefore, sufficient knowledge and vigilance in administering the vaccination will reduce the risk of AEFI. The immediate handling of side effects and reporting and recording of AEFI cases, improves the implementation of vaccination programs also reduces the risk of AEFI, and increase public confidence in the safety and benefits of vaccination. Additionally, research on mRNA-1273 booster vaccination is expected to support the implementation of the COVID-19 vaccination program in Indonesia. Based on the results, administering the third dose of mRNA-1273 vaccine is expected to provide better protection against COVID-19 infection. This study had limitations in that respondents were homogenous, while another AEFI might occur in different populations. However, our study is the first study that carried out among the early adult age group, second limitation is our study only assessed seven days of follow-up after vaccination while, long-term follow-up is needed to assess late symptoms of vaccination.

4. CONCLUSION

In conclusion, we found that the AEFIs booster mRNA-1273 vaccine in clinical clerkship students at Syarif Hidayatullah State Islamic University Jakarta was generally mild and did not require treatment. Furthermore, AEFI does not have a significant relationship with gender, history of allergies, comorbidities, or history of COVID-19 infection. This research shows that the safety of the mRNA-1273 booster vaccination, especially in the early adulthood age group, can provide better protection against COVID-19 infection and support the implementation of the COVID-19 vaccination program in Indonesia. It is hoped that this research can increase public confidence in the safety and benefits of vaccination. Our study is the first study conducted in the early adulthood age group. This study of administering the third dose of the AEFI-related mRNA-1273 vaccine in early adulthood provides the latest information on better protection against COVID-19 infection. Further research regarding long-term follow-up using a larger sample size and varying ages is recommended.

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