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Adverse events following immunization with COVID-19 vaccines

Eventos adversos después de la inmunización con vacunas contra COVID-19

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SUMMARY

Objective: *The purpose of this study was to identify Post-Vaccination Adverse Events (PVAE) with Moderna vaccine, locally systemically, and other reactions.*
Methods: *A quantitative descriptive research method with a retrospective approach was used in this study. The study was carried out at RSUD Cicalengka Bandung with a population of employees who had received the Moderna vaccine after two complete doses of Sinovac from August to September 2021. Purposive sampling was used, with a total of 162 respondents calculated using the Yamane formula.*
Result: *The results of this study showed that all respondents (100 %) had experienced PVAE after Moderna vaccination. The PVAEs were classified as systemic (95.1 %), local (92.6 %), and other (53.1 %). Fever (75.9 %) in systemic PVAEs, pain (92 %) in local PVAEs, and lymphadenopathy (25.9 %) in other PVAEs had the highest percentage of reactions. A significant proportion of respondents (27.5 %) reported being unable to work following the Moderna vaccination.*
Conclusions: *PVAE can occur following Moderna vaccination and result in the inability to work, potentially causing service problems. Employees must be scheduled for planned vaccinations and monitored for PVAE to reduce the possibility of adverse effects.*

Keywords: *COVID-19, COVID-19 Vaccine PVAE, Moderna Vaccine, mRNA.*

RESUMEN

Objetivo: *El propósito de este estudio fue identificar los Eventos Adversos Post vacunación (EAPV) con la vacuna Moderna, a nivel sistémico y otras reacciones.*
Métodos: *En este estudio se utilizó un método de investigación cuantitativo descriptivo con enfoque retrospectivo. El estudio se llevó a cabo en RSUD Cicalengka Bandung con una población de empleados que habían recibido la vacuna Moderna después de dos dosis completas de Sinovac de agosto a septiembre de 2021. Se utilizó un muestreo intencional, con un total de 162 encuestados calculados utilizando la fórmula de Yamane.*
Resultados: *Los resultados de este estudio mostraron que todos los encuestados (100 %) habían experimentado EAPV después de la vacunación con Moderna.*

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Los EAPV se clasificaron en sistémicos (95,1 %), locales (92,6 %) y otros (53,1 %). La fiebre (75,9 %) en los EAPV sistémicos, el dolor (92 %) en los EAPV locales y las adenopatías (25,9 %) en los demás EAPV fueron los que mayor porcentaje de reacciones que se presentaron. Una proporción significativa de los encuestados (27,5 %) informó que no podía trabajar después de la vacunación con Moderna.

Conclusiones*: EAPV puede ocurrir después de la vacunación con Moderna y dar como resultado la incapacidad para trabajar, lo que podría causar problemas en el servicio. Los empleados deben ser programados para vacunas planificadas y monitoreados para PVAE para reducir la posibilidad de efectos adversos.*

Palabras clave: *COVID-19, Vacuna COVID-19, EAPV, Vacuna Moderna, ARNm*

INTRODUCTION

Coronavirus Disease (COVID-19) is one of the health issues that threaten and concerns the world today. COVID-19 is an infectious disease caused by SARS Coronavirus 2 (SARS-CoV-2), a new type of coronavirus that has never been previously identified in humans. On December 31, 2019, the first case of COVID-19 was discovered in Wuhan City, Hubei Province, China. COVID-19 was declared a pandemic, on March 11, 2021. As of October 17, 2021, there were 240 239 218 confirmed COVID-19 cases worldwide, with 4 892 690 deaths; in Indonesia, there were 4 234 758 cases with 142 952 deaths. With a total of 704 470 cases and 14 666 deaths; Task Force for Handling COVID-19, 2021, West Java became the province with the second-highest incidence after DKI Jakarta. Meanwhile, there were 33 973 cases in Bandung Regency, with 608 deaths (1,2).

The increase in morbidity and mortality in COVID-19 is one of the harmful effects that can occur if this disease is not handled properly. COVID-19 has a broad impact on various aspects of life, in addition to having an impact on physiological aspects. COVID-19 influences the psychosocial and psychological systems (3,4). Another effect is the decline in performance in several health programs. This is due to the urgency of dealing with the COVID-19 pandemic, as well as public and officer concerns about COVID-19 transmission. The COVID-19 pandemic has even resulted in temporary closures and/or delays of health services in some areas, particularly at *Posyandu* (Integrated Healthcare Center) and health centers.

Along with the development of research and technology, scientists have succeeded in developing a COVID-19 vaccine as part of the management of the COVID-19 pandemic. The COVID-19 vaccination is one of the efforts that is considered quite effective in preventing and controlling this disease. The COVID-19 vaccination is aimed to reduce the transmission of COVID-19 (5), reduce morbidity and mortality due to COVID-19, and accelerate the formation of *herd immunity*. The type of COVID-19 vaccine used in Indonesia is the COVID-19 Vaccine PT. Bio Farma (Persero), AstraZeneca, China National Pharmaceutical Group Corporation (Sinopharm), Moderna, Novavax Inc, Pfizer Inc. and BioNTech, and Sinovac Life Sciences (6).

Moderna vaccine is an *mRNA-based platform* considered effective in preventing morbidity and mortality due to COVID-19 with 94.1 % efficacy. According to the completeness and accessibility of data obtained from phase III clinical trials, the Moderna vaccine (*mRNA*-1273) is one of the best choices for COVID-19 vaccines other than *BNT162b2* (Pfizer-BioNTech) with a record of being supported by economic and organizational availability. According to the Indonesian Food and Drug Authority (*Indonesian: Badan Pengawas Obat dan Makanan, lit.'Agency for Drug and Food Control'*) or *Badan POM/BPOM* Agency Study, the Expert Team of the National Committee for Assessing the COVID-19 Vaccine, and the *Indonesia Technical Advisory Group on Immunization* (ITAGI) in general the Moderna vaccine can be tolerated, both local and systemic reactions with severity *grades* 1 and 2. Local and systemic reactions that occur are one of the Post-Vaccination Adverse Events (PVAE) in the administration of the Moderna vaccine. PVAE is a medical event that is suspected to be related to vaccination, which can be in the form of a vaccine reaction, procedural error, accident, anxiety reaction, or an undetermined causal relationship. When compared to other types of COVID-19 vaccines, the COVID-19 vaccine with the mRNA platform, particularly Moderna, had the highest PVAE (7).

Several studies have suggested that the Moderna vaccination has side effects. According to the results of a study of 599 German health workers, 88.1 % reported at least one side effect, including injection site pain (75.6 %), headache (53.6 %), muscle pain (33.2 %), malaise (25 %), chills (23 %), and joint pain (21.2 %) (8). In all age groups and sexes, reactions to the cardiovascular system revealed hypertension, severe hypertension, supraventricular tachycardia, sinus tachycardia, and palpitations. Certain age or sex groups have had abnormal electorcardiographic (ECG) findings with elevated C-reactive protein, D dimer, and troponin. Acute myocardial infarction, cardiac arrest, and circulatory collapse are associated with vaccines in the >75-year age group. The use of vaccines with *mRNA -based platforms* have also been reported in cases of anaphylactic reactions and myocarditis (9,10).

Given the potential side effects of the Moderna vaccine as well as their consequences, it is deemed necessary for organizers of vaccination activities to monitor and deal with any PVAEs that may occur. After two complete doses of Sinovac, Cicalengka Hospital employees received the Moderna vaccine (booster). Further research on the possible side effects of Moderna vaccination is needed, so this study was conducted by the title: "Descriptive Study of Adverse Events Post Moderna Vaccination in Cicalengka Regional General Hospital Employees".

METHODS

A quantitative descriptive research method with a retrospective approach was used in this study. The study was carried out at RSUD Cicalengka Bandung with a population of employees who had received the Moderna vaccine after two complete doses of Sinova from August to September 2021. Purposive sampling was used, with a total of 162 respondents calculated using the Yamane formula.

In this study, each respondent used social media communication networks to complete an online based "KIPASS" questionnaire. KIPASS, which stands for PVAE Assessment, is a research instrument used to evaluate post-COVID-19 Vaccination Adverse Events. Researchers created KIPASS by identifying the results of PVAE observations from various sources (11-13). The "KIPASS" questionnaire consists of ten main questions about possible reactions to the COVID-19 vaccination. The number of participants in the validity test was 115, with the degree of freedom (df) = n-2 being 113, at a significance level of 5 %, and the number r table being 0.1832. This questionnaire has a validity value of 0.252 to 0.472 and a reliability value of 0.706 points.

This research has received ethical approval from the Research Ethics Committee of the University of 'Aisyiyah Bandung No.87/KEP.01/UNISA-BANDUNG/I/2022 dated January 17, 2022.

RESULTS

The demographic characteristics of the respondents are shown in Table 1. In effect, 46.9 % of respondents are aged 26-35 years, 62.3 % are female, and 74.7 % of them work as health workers at Cicalengka Hospital. Most of the vaccinated participants (63.6 %) were in good health and had no history of illness before receiving the COVID-19 vaccination. In this study, 100 % of all respondents (162/162) complained 15 minutes to 7 days after receiving the Moderna vaccination (Table 2). Each respondent experienced one or more groups of PVAEs. Of the 162 respondents studied, 150 respondents (92.6 %) experienced Local PVAEs, 154 respondents (95.1 %) experienced Systemic PVAEs, and 86 respondents (53.1 %) experienced Other PVAEs (Table 3). Moderna vaccination gives a higher reaction to Systemic PVAEs compared to Local PVAEs and Other PVAEs.

The following tables show the type of reaction felt by each PVAE group. Local PVAE; 92.0 % pain, 33.3 % swelling, 17.9 % redness, and 4.3 % bruising (Table 4). Fever 75.9 %, chills 74.7 %, myalgia 66.0 %, fatigue 47.5 %, headache 35.8 %, and arthralgia 33.3 %; systemic PVAE (Table 5). Other PVAEs included lymphadenopathy (24.9 %), nausea/vomiting (8.6 %), palpitations/chest pain/tightness (3.1 %), cellulitis (2.5 %), and allergic reactions (1.9 %). Drowsiness and syncope were both 0.6 % (Table 6).

Table 1. Frequency Distribution of Respondents' Characteristics

No	Characteristics	Criteria	Frequency	%
1	Age	17-25 yr	11	6.8
		26-35 yr	76	46.9
		36-45 yr	54	33.3
		46-55 yr	17	10.5
		56-65 yr	4	2.5
2	Gender	Man	61	37.7
		Woman	101	62.3
3	Profession	Medical Employee	121	74.7
		Non-Medical Employee	41	25.3
4	Respondent's Health History	No history of illness	103	63.6
		Asthma	6	3.7
		COVID-19	23	14.2
		Hypertension	7	4.3
		Liver Disorder	1	0.6
		Immunological Disorders	2	1.2
		Heart disease	1	0.6
		Allergy History	19	11.7

Note: Vaccination history of respondents V1 ,V2 Sinovac + V3 Moderna | IBM SPSS 20 output

Table 2. Frequency distribution of PVAE Moderna based on the presence or absence of PVAE

No	Characteristics	Criteria	Frequency	%
1	PVAE	Complaints 15 minutes to 7 days after Moderna vaccination	162	100.0
2	Non-PVAE	No complaints 15 minutes to 7 days after Moderna vaccination	0	0.0
	Total		162	100.0

Note: Vaccination history of respondents V1, V2 Sinovac + V3 Moderna | IBM SPSS 20 output

Table 3. Frequency Distribution of PVAE Moderna Based on PVAE Classification

No	Characteristics	Criteria	Frequency	%
1	Local PVAE	Yes	150	92.6
		Not	12	7.4
2	Systemic PVAE	Yes	154	95.1
		Not	8	4.9
2	Other PVAEs	Yes	86	53.1
		Not	76	46.9

Information: each respondent can experience more than one type of group PVAE

Local PVAE	Experiencing local reactions, there is at least 1 “Yes” answer from 4 local reactions; pain, swelling, redness, and bruising
Systemic PVAE	Experiencing a systemic reaction (total), there is at least 1 answer "Yes" out of 6 systemic reactions; chills, fever, *fatigue*, *myalgia*, *arthralgia*, *and headache*
Other PVAEs	Experiencing other reactions, in addition to local and systemic reactions

IBM SPSS 20 output

Table 4. Frequency Distribution of Moderna Local PVAEs

No	Local PVAE	Criteria	Frequency	%
1	Painful	Yes	149	92.0
		Not	13	8.0
2	Swollen	Yes	54	33.3
		Not	108	66.7
3	Redness	Yes	29	17.9
		Not	133	82.1
4	Bruises	Yes	7	4.3
		Not	155	95.7

IBM SPSS 20 output

Table 5. Frequency Distribution of Modern Systemic PVAEs

No	Local PVAE	Criteria	Frequency	%
1	Shivering	Yes	121	74.7
		Not	41	25.3
2	Fever	Yes	123	75.9
		Not	39	24.1
3	*Fatigue*	Yes	77	47.5
		Not	85	52.5
4	*Myalgia*	Yes	107	66.0
		Not	55	34.0
5	*Arthralgia*	Yes	54	33.3
		Not	108	66.7
6	Headache	Yes	58	35.8
		Not	104	64.2

IBM SPSS 20 output

Table 6. Frequency Distribution of Other Moderna PVAEs

No	Characteristics	Frequency	%
1	*Lymphadenopathy*	42	25.9
2	Cellulitis	4	2.5
3	Nauseous vomit	14	8.6
4	Palpitations/chest pain/shortness of breath	5	3.1
5	Allergic reaction	3	1.9
6	Sleepy	1	0.6
7	Syncope	1	0.6
8	Not	92	56.8
Total	162	100.0	

IBM SPSS 20 output

The length of a Moderna PVAE Day is shown in Table 7 by time interval: 1-2 days, 3-4 days, 5-7 days, and >7 days. Most complaints (87.3 %) last only 1-2 days.

Table 8 shows the impact of PVAE; the majority of RSUD Cicalengka employees were not affected by the perceived PVAE (48 %), 28.4 % of them left their duties due to sick leave, and the rest said they might be affected by 23.5 %.

Table 7. Distribution of Modern PVAE Days

No	Characteristics	Local PVAE		Systemic PVAE		PVAE Moderna	
		freq	%	freq	%	freq	%
1	1-2 days	184	77.0	496	91.9	680	87.3
2	3-4 days	41	17.2	35	6.5	76	9.8
3	5-7 days	14	5.9	9	1.7	23	3.0
4	>7 days	0	0.0	0	0.0	0	0.0
5	Total	239	100.0	540	100.0	779	100.0

IBM SPSS 20 output

Table 8. Frequency Distribution of Moderna PVAE Impact on

No	Characteristics	Criteria	Frequency	%
1	Sick Leave (leaving work)	Not	78	48.1
		Yes	46	28.4
		Maybe (The peak of complaints occurs during work holidays)	38	23.5
	Total		162	100.0

DISCUSSION

In this study, a person was diagnosed with local PVAE if he experienced pain, swelling, redness, or bruising at the injection site. According to the results of a descriptive study of Moderna PVAE in Cicalengka Hospital employees, local PVAEs occurred in 92.6 % (150/162). The most common complaint after COVID-19 vaccination was pain (92.0 %), followed by swelling (33.3 %), redness (17.9 %), and bruising (4.3 %).

An effective vaccine provides an antigen source and contains an adjuvant to induce strong up-regulation of costimulatory molecules in host dendritic cells (DC). Adjuvants operate by producing IFN-1 (interferon type 1). The adverse effects of COVID-19 may be related to the high production of IFN-1 and the inducing of an effective immune response. IFN-1 is substantially more potent in women than men and at younger than older ages. IFN-1 production after COVID-19 vaccination was higher than after infection with SARS-CoV-2. This could explain why young people and the female sex tend to have substantial adverse effects on the COVID-19 vaccine (14).

The characteristics that influenced post-vaccination adverse events in 8 countries, said there was a significant variation in post-vaccination adverse events based on age group and sex (15). In another study, gender and age did not significantly correlate with post-vaccination follow-up events. However, a history of COVID-19 illness was significantly associated with the Severity of Side Effects for complaints of local reactions and fatigue (16,17).

Moderna post-vaccination pain was 92.0 % same as the results of the Moderna vaccine clinical trial in a study at Cicalengka Hospital. When compared to the results of studies/research conducted 62.8 %, and 75.6 %, the results of this study were higher. Conducted a similar study on health workers at the port of Semarang, Central Java, who received two complete doses of Sinovac plus one booster dose of Moderna; the incidence of pain was 100 % higher than the results of the Cicalengka Hospital study (18).

The pain was induced in the Moderna vaccination by a needle stick wound and the Moderna vaccine's reaction. The injection technique (19) and the condition of the needle used in terms of length-diameter size, and level of sharpness (20), also influence pain after vaccination. The needle used for Moderna vaccination was an Auto Disable Syringe (ADS) or a 1 mL (25g, 0.5 mm diameter) or 3 mL (23g, 0.6 mm diameter) syringe depending on the availability of facilities and applications using the same needle between vaccine collections using vials and intramuscular injections (21). Pain is also influenced by each respondent's subjective and very individual perception, as evidenced by the value of pain felt by respondents on a scale of 0-10. The results showed that most of the respondents gave a score of 5 on a scale of 0-10 for the pain they felt (an average of 5,9). The results of this study were higher than the results of the Moderna vaccine clinical trial (22-24).

According to the results of a descriptive study conducted by PVAE Moderna on Cicalengka Hospital employees, 54 respondents (33.3 %) reported swelling at the injection site. This result was higher than previous studies' results of 14.7 % and 18.5 %, respectively. Swelling is defined as a temporary abnormal enlargement or volume increase in a body part that is not caused by cell proliferation. Swelling at the injection site occurs because of a physiological reaction to the vaccine agent that is injected into the body (25-27).

According to the results of a descriptive study conducted by PVAE Moderna on Cicalengka Hospital employees, 29 out of 162 respondents (17.9 %) reported redness at the injection site. The results of the study in Cicalengka Hospital were consistent with clinical trials and previous studies. Based on the results of a descriptive study conducted by PVAE Moderna on Cicalengka Hospital employees, bruising was reported by 7 out of 162 respondents (4.3 %). It is the respondent's weakest reaction. The incidence of bruising was not determined during the clinical trial phase or in previous studies related to Moderna vaccination, but bruising was identified as a reaction related to immunization/vaccination procedures, specifically PVAE caused by insufficient vaccine handling methods (28-30).

A bruise (hematoma) is a blood extravasation beneath the skin caused by trauma. Deep hematomas are blue with a diameter greater than 1 cm, whereas superficial hematomas are red (31). Bruising is a local reaction that can occur with any injection; it is related to the injection technique as well as the sharpness of the needle used (31). Concerning COVID-19 vaccination, bruising has been related to thrombocytopenia with injection site trauma in individuals who received m-RNA and vector-based vaccination (32-35).

A person is diagnosed with systemic PVAE if they have chills, fever, weakness/fatigue (fatigue), muscle pain (myalgia), joint pain (arthralgia), and/or headache. According to the results of a descriptive study of Moderna PVAE in Cicalengka Hospital employees, systemic PVAEs occurred 95.1 % of the time (154/162). The most common complaints following the Moderna vaccination were fever (75.9 %) and chills (74.7 %). Infectious disease viruses stimulate the formation of intracellular spike proteins, triggering an immune response. This process is directly related to the emergence of the headache phenotype, as well as associated symptoms such as fatigue, chills, weakness, joint pain, and dizziness. Microorganisms may be able to activate anti-inflammatory substances such as nitric oxide, prostaglandins, and cytokines (36-38).

Fever is the body's natural reaction to vaccination agents. Fever should not be prevented by giving prophylactic antipyretics before vaccination because it will reduce the body's response to the formation of antibodies. Post-vaccination antipyretic drugs will decrease the response to the increase in body temperature required to induce the vaccine. In certain conditions that require taking antipyretic drugs, antipyretic drugs may be given 4 hours after vaccination (39,40).

According to the findings of the PVAE Moderna descriptive study on Cicalengka Hospital employees, the incidence of fatigue was 47.5 % (77/162), which was consistent with the findings of who found fatigue in respondents who were given the vaccine. The exact mechanism of weakness following COVID-19 vaccination, including the Moderna vaccine, is unknown. However, in cases of COVID-19 infection caused by SARS-CoV-2, weakness is common. The formation of intracellular spike proteins triggering an immune response and activating anti-inflammatory substances such as nitric oxide, prostaglandins, and cytokines, causes weakness in COVID-19 infection (41).

The weakness in COVID-19 is caused by several factors; 1) Factors affecting the central nervous system because of frontal hypometabolism and cerebellar hypermetabolism; 2) Anxiety and fear-related psychological factors; 3). A peripheral factor associated with disturbances in muscle metabolic homeostasis caused by cytokines and interleukin-6 release (42).

CONCLUSION

Based on the results of a descriptive study of post-Moderna vaccination follow-up events in Cicalengka Hospital Bandung employees, it can be concluded that of the 162 respondents who received the 3rd dose of booster vaccination using the Moderna vaccine, all of them experienced complaints 15 minutes to 7 days after Moderna vaccination. Based on the classification, the results of the study showed that local PVAEs were 92.6 %, systemic PVAEs were 95.1 % and other PVAEs were 53.1 %.

Local PVAEs include pain 92.0 %, swelling 33.3 %, redness 17.9 %, and bruising 4.3 %. Systemic PVAEs include fever 75.9 %, chills 74.7 %, *myalgia* 66.0 %, *fatigue* 47.5 %, *arthralgia* 33.3 %, and *headache* 35.8 %. Other

PVAEs, namely post-vaccination Moderna complaints, include swelling/pain in the injected armpit area (lymphadenopathy) 25.9 %, nausea/vomiting 8.6 %, cellulitis 2.5 %, allergic reactions 1.9 %, heart palpitations (palpitations)/chest pain/tightness 3.1 %, drowsiness 0.6 %, and fainting (syncope) 0.6 %. The majority of PVAE lasts 1-2 days (87.3 %). The systemic PVAE group (91.9 %) frequently reported PVAE that lasted 1-2 days.

PVAEs have an impact on the ability to carry out tasks and have the risk of disrupting services. 27.5 % of employees reported leaving their jobs to take sick leave, rest, or seek treatment. Because the peak of complaints occurred during work holidays, 25.7 % reported that they might leave work (sick leave).

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