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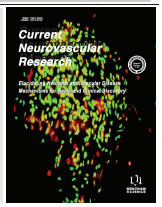
CASE REPORT

Acute Ischaemic Stroke Incidence after Coronavirus Vaccine in Indonesia: Case Series



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Abstract: ***Background*:** Coronavirus disease-19 (COVID-19) is an infectious disease with high morbidity and mortality rates. Indonesia had reported a 2.8% of mortality rate up to June 2021.

***Case Presentation*:** A strategy to control the virus spreading is by vaccination. The Indonesian Food and Drug Monitoring Agency had approved the use of CoronaVac, an inactivated virus vaccine developed by Sinovac. Most Adverse Events Following Immunization (AEFI) for CoronaVac are mild, and the most common symptoms are injection-site pain, headache, and fatigue. Neurovascular adverse events, including thrombosis or ischaemic stroke after receiving CoronaVac have not previously been reported.

***Conclusion*:** Correspondingly, we reported three patients with an Acute Ischaemic Stroke (AIS) after the administration of CoronaVac in our hospital.

Keywords: CoronaVac, COVID-19, stroke, vaccine, AEFI, COVID 19.

1. INTRODUCTION

COVID-19 was first reported in Wuhan, China, in December 2019 as an infectious disease caused by Novel Coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since the first reported case in China, the disease had rapidly spread around the world [1, 2]. The first case in Indonesia was first reported in March 2020, and the case keeps increasing. The Ministry of Health of Indonesia had reported 1.894.025 confirmed cases with a 2.8% fatality rate up to June 11, 2021 [3, 4].

The spread of this highly contagious virus needs to be controlled, one of which is by vaccination. In January 2021, The Indonesian Food and Drug Monitoring Agency had officially approved the use of CoronaVac, an inactivated virus vaccine developed by Sinovac, for the Emergency Use Authorization (EUA). The CoronaVac is given in two doses within the second dose injected, ranging from 14-28 days after the first dose [5].

CoronaVac is considered safe and effective when used properly. According to Indonesian authorities, the phase three clinical trial of the CoronaVac vaccine in Bandung demonstrated 65.3% efficacy. However, this vaccine can also cause adverse events, called Adverse Events Following Immu-nization (AEFI). AEFI is defined as medical events that occur after immunization (≤28 days), including vaccine reactions, injection, procedural errors, or coincidences until a causal relationship is determined [6]. Adverse events following the CoronaVac vaccine were reported divided into local reactions such as local pain, redness, induration, swelling, and systemic events including fever, fatigue, and myalgia. Phase three of the clinical trial conducted in Indonesia, Turkey, and Brazil, reported that there was only one adverse event in Turkey, which was an allergy. [7].

Mortality rates after the CoronaVac vaccine have been reported in several countries. There were 27 deaths reported in Indonesia after the CoronaVac vaccine. However, the National Commission of AEFI said these deaths were not related to vaccination. From a total of 27 people, 10 people died due to COVID-19 infection, 14 people died from cardiovascular disease, 1 person died from acute kidney failure, and 2 others died from uncontrolled hypertension and diabetes mellitus [8].

To date, there has not been any report of thrombosis or acute ischemic stroke after receiving the CoronaVac vaccine. In this report, we present three cases with acute ischemic stroke after the administration of the CoronaVac vaccine. They were hospitalized in Universitas Indonesia Hospital with neurological manifestation after the first dose of the CoronaVac vaccine.

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2. CASE ILLUSTRATION

2.1. Patient 1

A hypertension 77-year-old male with coronary artery disease (CAD), diabetic Mellitus (DM) type two and a history of ischemic stroke in 2016 presented approximately 90 minutes following the first dose of the CoronaVac vaccine. Clinical manifestations of stroke in this patient were slight left leg motor weakness and slurred speech (National Institute of Health Stroke Scale (NIHSS) 1) with onset-to-door time (ODT) being one day. These neurological deficits occurred previously. Investigation showed rapid test antigen COVID-19 negative, average blood count level and elevated blood sugar level; normal X-ray chest; computed tomography (CT) brain showed multiple infarcts in bilateral centrum semiovale, cortical-subcortical right frontal and temporal lobe, bilateral external capsule, and right pons with Fazekas grade 2. The patient received a double antiplatelet and was discharged after being hospitalized for four days with a modified Rankin score (mRS) of 1.

2.2. Patient 2

A 79-year-old male, ex-smoker with hypertension, presented two days following the first dose of the CoronaVac vaccine. Clinical manifestation in this patient was left hemiparesis (NIHSS 3) with ODT being two days. Investigation showed rapid test antigen COVID-19 negative, normal blood count level, elevated blood sugar level and total cholesterol level; X-ray chest showed mild cardiomegaly; Magnetic Resonance Imaging (MRI) ofthe brain showed lacunar infarct hyperacute-acute phase in the right frontoparietal with Fazekas grade 2. The patient received aspirin and was discharged on the fifth day with mRS of 1.

2.3. Patient 3

A 62-year-old male, with hypertension with a history of ischemic stroke in 2017, presented one day following the first dose of the CoronaVac vaccine. Clinical manifestations in this patient were left hemiparesis, slurred speech, and facial asymmetry (NIHSS 4) with ODT being three days. Investigation showed negative rapid test antigen COVID-19, no remarkable laboratory results; normal X-ray chest; brain MRI showed acute deep watershed infarction in right centrum semiovale and corona radiata, chronic lacunar infarct right centrum semiovale and bilateral corona radiata with Fazekas grade 3. The patient received a double antiplatelet and was discharged after 12 days with mRS of 1 (Table **1**).

3. DISCUSSION

Ischemic stroke accounts for about 80% of stroke incidence. The incidence of ischemic stroke increases with age, hypertension, smoking status, diet, physical inactivity, hyperlipidemia, diabetes mellitus, cardiac causes, obesity (central obesity), and alcohol consumption [9]. All the patients were elderly (>60 years old) and suffered from uncontrolled hypertension, and they did not take any medicine to treat their hypertension after being vaccinated. Untreated hypertension was predicted to be responsible for 28% of all incidence strokes in the general population. Meanwhile, in treated patients, uncontrolled blood pressure was found to be responsible for 45% to 52% of incidence strokes [10]. Moreover, two of three patients had a history of stroke, which made the risk of recurrent stroke increased by 11.3% at five years [11].

Three cases presented had an acute ischemic stroke, ranging from 30 minutes to two days following the first dose of the CoronaVac vaccination. The symptoms appeared in less than 28 days after vaccination, so it can still be categorized as AEFI. All patients did not seek emergency help when acute neurological deficits occurred. They came to the hospital after the symptoms appeared in more than 24 hours. This phenomenon might be caused by a lack of awareness regarding its mild clinical manifestations.

All patients presented mild symptoms with NIHSS ranging from 1 to 4. Clinical manifestation in all patients was left hemiparesis and slurred speech, one patient also had facial asymmetry. Based on TOAST classification, there were several subtypes of ischemic stroke, from large-artery atherosclerosis to undetermined etiology. In addition, the three patients had different mechanisms of stroke. Since patient 1 had a history of hypertension, diabetes, and CAD, he could develop multiple thrombosis in several intracranial vessels due to the atherosclerosis process. Patient 2 suffered from small vessel disease, as it was seen in the brain MRI [12]. The last patient had an internal watershed infarction caused by hemodynamic compromise or stenosis due to atherosclerosis [13]. Laboratory results showed high blood glucose in all patients with normal platelet count and normal D-dimer in patient 3.

The Fazekas scale was used to identify white matter T2 hyperintense lesions size associated with chronic small vessel ischemia. Patients with a Fazekas scale of 0-1 were classified as mild white matter disease (WMD), while with a scale of 2-3 were classified as severe WMD. The severity of WMD is related to recurrent stroke and functional outcome after ischemic stroke [14]. In this research, the Fazekas scale in all patients ranged from 2 to 3, indicating severe WMD.

The three patients received double and single antiplatelet. Double antiplatelets (aspirin and clopidogrel) were given to patients 1 and 3 to reduce the risk of recurrent stroke. According to Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial, a combination of clopidogrel and aspirin would inhibit platelet aggregation simultaneously and reduce the risk of recurrent stroke by 32%, compared to aspirin in individuals with mild ischemic stroke [15]. Double antiplatelet should be given early within 12-24 hours or maximum 7 days after symptom onset, continued for 21-90 days and followed by long-term single antiplatelet [9].

Vaccination is an effective method to control infectious diseases. However, the occurrence of AEFI is hard to predict on every individual yet can be minimized by following contraindications of each vaccine. Uncontrolled hypertension

Table 1. Clinical characteristics of the patients.

Characteristics	Patient 1	Patient 2	Patient 3
Age	77-year-old	79-year-old	62-year-old
Gender	Male	Male	Male
Medical history:			
HTN	Yes	Yes	Yes
History of ischemic stroke	Yes	No	Yes
CAD	Yes	No	No
DM type 2	Yes	No	No
Smoke	No	Yes	No
Blood pressure in ER	168/79 mmHg	165/75 mmHg	150/90 mmHg
Stroke onset	90 min	2 days	1 day
Onset to door	1 day	2 days	3 days
Clinical manifestation:			
LT hemiparesis	Yes	Yes	Yes
Slurred speech	Yes	Yes	Yes
Facial asymmetry	No	No	Yes
NIHSS on admission	1	3	4
Lab results:			
NLR	1.92	3.67	3.59
Platelet (^10^3/μL)	237	295	181
Blood glucose (mg/dL)	183	150	179
D-dimer	No data	No data	305.62
Antigen rapid test	Negative	Negative	Negative
Imaging:			
Lacunar infarct	Yes	Yes	Yes
Leukoaraiosis	Yes	Yes	Yes
Fazekas	2	2	3
Treatment received	DAPT	Aspirin	DAPT
mRS	1	1	1

ER (Emergency Room), ***HTN(***Hypertension), ***DM(***Diabetes Mellitus), ***NLR*** (Neutrophil Lymphocyte Ratio), ***LT*** (Left), **DAPT (**Double Antiplatelet), **SAPT** (Single Antiplatelet), ***mRS*** (Modified Rankin Score). NLR = normal value 1-3, platelets = normal value 250.000-450.000, blood glucose = normal levels up to 140 mg/dL, D-dimer = normal value up to 500 ng/dL.

(blood pressure ≥180/110) and uncontrolled diabetes mellitus (blood glucose >250 or acute metabolic condition) are contraindications to CoronaVac injection. Patients who have risk factors such as hypertension and/or diabetes mellitus should be controlled before and after vaccination. If the comorbidities are still not controlled before vaccination and became one of the contraindications, the vaccination can be postponed until the conditions meet the vaccination criteria [16].

Thrombosis incidence has been reported with the use of the Oxford-AstraZeneca vaccine (ChAdOx1). These events are called vaccine-induced thrombotic thrombocytopenia (VITT) and were first reported in April 2021 [17]. Some thrombosis events have been reported, including cerebral venous sinus thrombosis (CVST), acute ischemic stroke, limb ischemia, pulmonary artery thrombosis, and splanchnic vein thrombosis. The mechanism that underlies this event is antibodies, usually immunoglobulin G (IgG), and against platelet factor 4 (PF4) complexes. VITT was also reported in patients who received the Ad26.CoV2.S vaccine (Johnson & Johnson-Janssen) but not in those who received the CoronaVac vaccine [18]. All three cases also did not show any thrombocytopenia nor thrombocytosis.

Currently, there are no studies that stated that the CoronaVac vaccine would increase blood pressure and blood sugar that can lead to neurovascular events, including ischemic stroke. Due to the scarce evidence or report of CoronaVac AEFI, it is unsure whether the acute ischemic stroke was related to vaccination. Thus, this result should be interpreted wisely. Moreover, as many countries are struggling to increase the vaccination coverage, some AEFI reports could bring distrust or discomfort among people who are willing to get vaccinated. More studies are needed to further validate these findings with the increase of vaccine coverage andthe variety of vaccines used in each country with reported AEFIs.

CONCLUSION

Vaccination is one of the most effective methods to control life-threatening infectious diseases. AEFI can be minimized by following the contraindications of each vaccine.

However, acute ischemic stroke following the CoronaVac vaccination has been treated by antiplatelet. There is no different guideline to treat these cases. Therefore, acute ischemic stroke as AEFI of the CoronaVac vaccine needs further investigation.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Written informed consent was received from the precipitates.

STANDARDS OF REPORTING

CARE guideline were followed.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available on request from the corresponding author.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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