Incidence and Clinical Characteristics of Acute Ischemic Stroke or Transient Ischemic Attack following Whole Cell COVID-19 Vaccination (CoronaVac) in Southern Thailand

Adithep Leevattananukool
Suwanna Setthawatcharawanich

ABSTRACT

Objective: To report (1) the incidence and (2) clinical characteristics of acute ischemic stroke (AIS) or transient ischemic attack (TIA) after CoronaVac vaccination in Southern Thailand

Background: In late 2019, there was a pandemic of COVID-19 infection worldwide. In February 2021, Department of Disease Control of Thailand announced that CoronaVac (by Sinovac Biotech) was a first vaccine approved for emergency use authorization. AIS, a rare vaccination-related event was reported in many COVID-19 vaccines. However, there was limited data of post-vaccination ischemic stroke related to CoronaVac.

Materials and Methods: This is a multicenter study including 12 medical centers which had neurologist in Southern Thailand. The study included patients with 18-years old or more who developed AIS or TIA after CoronaVac vaccination between April and July 2021. Acute ischemic stroke or TIA was diagnosed by neurologist according to clinical manifestations occurring within 30 days post-vaccination and brain imaging was done. The clinical characteristics were described. The incidence was analyzed as events per 1,000,000 doses.

Results: There were 68 patients who developed AIS or TIA after CoronaVac vaccination which accounted for an incidence of 177.3 events per 1,000,000 doses. Most of the patients were female (79.4%) with median age of 35.5 years (IQR, 29-42.5). The most common manifestations were numbness (80.8%), followed by weakness (42.6%), dysarthria (8.8%) and facial palsy (5.8%). The NIHSS 0-4 was found in 98.5%. Most of the patients recovered within 30 days.

Conclusions: The study reported an incidence of AIS or TIA after CoronaVac vaccination. The most common presenting symptom was hemi-sensory. The severity was mild and most of them recovered within one month.

Adithep Leevattananukool
Assoc. Prof. Suwanna Setthawatcharawanich
Neurology unit Department of Internal Medicine
Faculty of Medicine, Prince of Songkla University

Corresponding author:
Adithep Leevattananukool, MD.
Neurology unit Department of Internal Medicine
Faculty of Medicine, Prince of Songkla University
Mobile phone: 086-375-3910 E-mail : armmedswu30@gmail.com

รับต้นฉบับ 24 กุมภาพันธ์ 2567, ปรับปรุงต้นฉบับ 4 สิงหาคม 2567, ตอบรับต้นฉบับตีพิมพ์ 31 สิงหาคม 2567

Introduction and Objective

In late 2019, there was the pandemic of COVID-19 infection worldwide. Therefore, COVID-19 vaccination development program was the first priority globally to prevent the disease outbreak. Abundance of vaccine with many formulations were produced and distributed to inject for COVID-19 prevention[1,2]. In February 2021, Department of Disease Control of Thailand first-approved CoronaVac (Inactivated SARS-CoV-2 virus, by Sinovac Biotech) for emergency use authorization. The effectiveness of CoronaVac is approximately 65.9% for the prevention of COVID-19, and 86.3% for the prevention of COVID-19-related deaths[3].

Among rare vaccination related adverse events, acute ischemic stroke is one of serious adverse events reported in many of COVID-19 vaccines; ChAdOx1(Astrazeneca), mRNA-1273 (Moderna), BNT162b2 (BioNTech/Pfizer), and Ad26. COV2.S (Janssen)[4]. The stroke following these vaccinations was explained by vaccine-induced immune thrombotic thrombocytopenia (VITT)[5-7]. In Europe, the incidence of acute ischemic stroke after mRNA or non-replicating viral vector vaccine was vary between 12.2-65.3 events per 1 million doses of vaccination[8]. The data of post-vaccination ischemic stroke after CoronaVac administration was still limited[9]. The study aimed to report incidence and clinical characteristics of acute ischemic stroke (AIS) or transient ischemic attack (TIA) after CoronaVac vaccination in Southern Thailand.

Materials and Methods

This is a retrospective, descriptive, and multicenter study in Southern Thailand performed during April 2021 - July 2021. Healthcare centers which had neurologist and radiologist were invited to participate in the study. The inclusion criteria were patients with age of 18 years or more who developed acute ischemic stroke or TIA after CoronaVac vaccination within 30 days and underwent brain imaging (CT or MRI). Patients who received other vaccinations within 3 months, or neurological symptoms were better accounted for by another diagnosis besides acute ischemic stroke or those whom neuroimaging study suggested alternative diagnosis were excluded. Acute ischemic stroke or TIA was diagnosed by neurologist based on clinical symptoms and brain imaging[10] which was reported by radiologist in each center.

For imaging study, all patients underwent a 64 slide CT scan or 1.5 Testa MRI. Head CT included non-contrast axial and coronal plain. Head MRI sequences included axial Diffusion-weighted imaging (DWI), Apparent diffusion coefficient (ADC), T2-weighted, Fluid attenuated inversion recovery (FLAIR), T1-weighted, and sagittal T1-weighted.

Demographic and clinical data were collected. Stroke severity was graded by National and Institute of Health Stroke Scale (NIHSS) ranging from 0 to 42, the higher score indicating more severe neurologic deficit. Outcome was reported as Modified Rankin ScaleMRS (MRS) ranging from 0-6 (0= no symptoms at all, 1= no significant disability, 2= slight disability, 3= moderate disability, 4= moderately severe disability, 5= severe disability, 6= dead). The study was approved by the Institutional Ethics Committee, Faculty of Medicine, Prince of Songkla University.

Table 1 : Demographic and clinical data of patients with acute ischemic stroke or TIA after CoronaVac vaccination

a)

Characteristics	N=68
Sex -- no. (%)	
Female	54 (79.4%)
Male	14 (20.6%)
Age, Median -- (IQR), years	35.5 (29-42.5)
Medical history -- No. (%)	
None	35 (51.4%)
Has medical history	33 (48.5%)
- Hypertension	6/33 (18.1%)
- Dyslipidemia	5/33 (15.1%)
- Diabetes mellitus	4/33 (12.1%)
- Migraine	4/33 (12.1%)
- Old CVA	4/33 (12.1%)
Number of injected -- No. (%)	
1st injection	51/61 (83.6%)
2nd injection	10/61 (16.3%)
Missing data	7

b)

Clinical	N=68
Onset of symptoms -- no. (%)	
Less than 1 hour	30 (44.1%)
1-24 hour	21 (30.9%)
> 1 days – 30 days	17 (25%)
Clinical manifestation -- no. (%)	
Numbness	55 (80.8%)
Weakness	29 (42.6%)
Dysarthria	6 (8.8%)
Facial palsy	4 (5.8%)
NIHSS -- no. (%)	
0	12/67 (17.9%)
1	39/67 (58.2%)
2	6/67 (8.9%)
3	5/67 (7.5%)
4	4/67 (6%)
5	1/67 (1.5%)
Missing data	1
MRS outcome at follow up day -- no. (%)	
0	48/53 (90.6%)
1	5/53 (9.4%)
Missing data	15
Time to complete recovery (MRS 0) -- no. (%)	
Within 1 day	20/48 (41.6%)
Within 3 days	32/48 (66.6%)
Within 7 days	41/48 (85.4%)
Within 30 days	47/48 (97.9%)
> 30 days	1/48 (2.1%)
Missing data	20

- IQR : interquartile ranges, CVA : Cerebrovascular accident, NIHSS : National and Institute of Health Stroke Scale, MRS : Modified Rankin Scale

Statistical analysis

The demographic, clinical data and radiological data were described. Continuous variables were described as means and standard deviations or medians and interquartile ranges (IQRs), as appropriate. Categorical variables were expressed as counts and percentages. These data were adjusted in Microsoft Excel. The incidence was analyzed as events per 1,000,000 doses.

Results

Twelve medical centers in the southern part of Thailand participated in the study. Sixty-eight patients who developed AIS or TIA after CoronaVac vaccination, 54 (79.4%) were female and median age was 35.5 years (IQR, 29-42.5) (Table 1). Underlying medical problems were reported in 48.5% including hypertension (18.1%), dyslipidemia (15.1%), diabetes mellitus (12.1%), and history of old cerebrovascular events (TIA, ischemic stroke, hemorrhagic stroke) (12.1%). The symptoms that occurred after first vaccine injection were reported in 51 patients (83.6%).

Neurological symptoms occurring within 1 day after vaccination were reported in 75% and 44.1% of these had neurological deficit within 1 hour. The most common manifestations were numbness (80.8%), followed by weakness (42.6%), dysarthria (8.8%) and facial palsy (5.8%). The NIHSS at presentation was graded as 0 (17.9%), 1 (58.2%), 2 (8.9%), 3 (7.5%), 4 (6%) and 5 (1.5%). About 90% of the patients were full recovery (MRS= 0) and 98% of them had complete recovery within 30 days.

Brain CT scan was done in 85% (58 of 68) and showed normal in 86% of patients. The abnormalities findings were old lacunar infarction (25%) and hypodensity of uncertain nature (75%). MRI and MRA of the brain were done in 57.3% (39 of 68) and 39.2 % (26 of 68), respectively. Ninety-three percent of brain MRI in this group was done within 30 days. Brain MRI reported as acute infarction (positive DWI) in 10.2% (4 of 39). Brain MRA showed abnormalities in 23.1% ranging from mild irregularity to severe narrowing of intracranial vessels (Table 2).

Table 2 : Radiological reports of patients with AIS or TIA after CoronaVac vaccination

Imaging	N (%)
• **CT scan of the brain**	**58/68 (85.3%)**
- CT scan within 24 hours	17/58 (68%)
- Normal CT scan	50/58 (86.2%)
- Abnormal CT scan	8/58 (13.8%)
• **MRI scan of the brain**	**39/68 (57.3%)**
- MRI scan within 30 days	27/39 (93.1%)
- Normal MRI scan	29/39 (74.3%)
- Abnormal MRI scan	10/39 (25.7%)
Acute infarction	4/39 (10.2%)
White matter lesion	4/39 (10.2%)
Old infarction	1/39 (2.6%)
• **MRA of the brain**	**26/68 (39.2%)**
- Normal MRA scan	20/26 (76.9%)
- Abnormal MRA scan	6/26 (23.1%)
Mild narrowing blood vessel	3/26 (11.5%)
Moderate to severe narrowing blood vessel	3/26 (11.5%)

- CT : Computed Tomography, MRI : Magnetic Resonance Imaging, MRA : Magnetic Resonance Angiography

Four symptomatic patients whose MRI showed evidence of acute infarction were described in table 3. Half of them had symptoms within 24 hours and all patients had stroke phenomena within 5 days. Brain MRA of these patients showed moderate to severe narrowing of vessel which distributed to infarct area. Unfortunately, three patients had loss to follow up, except patient 3 had complete recovery within 30 days.

During April to July 2021, the government of Thailand distributed 383,520 doses of CoronaVac to Southern Thailand mainly for healthcare workers. The study reported 68 patients who developed AIS or TIA post-CoronaVac vaccination which accounted for an incidence of 177.3 events per 1 million doses administered.

Table 3 : Clinical manifestations and neuroradiological findings of patients with brain MRI shown evidence of acute infarction

	Patient 1	Patient 2	Patient 3	Patient 4
Medical center	Chumporn hospital	Chumporn hospital	HatYai hospital	Trang hospital
Age (years)	49	35	23	49
Sex	M	F	M	M
Medical history	Hypertension Dyslipidemia	Old stroke (Unknown subtype)	None	Diabetes mellitus Hypertension
BMI	28.6	N.R.	21.53	25
No. of injection	1	1	1	N.R.
Side of injection	Left	Left	N.R.	Left
Onset	2 days	30 minutes	5 days	8 hours
Blood pressure in ER	N.R.	165/93	109/59	116/70
Clinical	Rt.hemiparesthesia Rt.hemiparesis Gr.IV Dysarthria	Lt.hemiparesthesia Lt.hemiparesis Gr.IV	Rt.hemiparesthesia Rt.facial palsy Global aphasia	Rt.hemiparesthesia
NIHSS	2	3	5	1
MRI finding	acute lacunar infarction at posterior limb of Lt.internal capsule	acute infarction at Rt.posterior limb of internal capsule	acute infarction in Lt. MCA territory	acute infarction Lt.occipital lobe
MRA finding	severe narrowing of P4 of both PCA, moderate narrowing at temporal branch at Lt.MCA	moderate narrowing at clinoid part of Lt.ICA, severe narrowing at P4 segment of Rt.PCA	short segment of total occlusion/severe stenosis at distal M1segment of left MCA with moderate diminished branches in left MCA territory // mild irregularity of left carotid bulb	Not done
Outcome	N.R.	N.R.	Full recovery at 1st F/U visit (18days)	N.R.

- MRI : Magnetic Resonance Imaging, MRA : Magnetic Resonance Angiography; Sex : M as male, F as female; BMI : Body-mass index (the weight in kilograms divided by square of the height in meters); Rt. : Right, Lt. : Left; Gr. : Grade (Motor power grading assess with Medical Research Council's scale, 0 as No contraction, 1 as Flicker or trace of contraction, 2 as Active movement with gravity eliminated, 3 as Active movement against gravity, 4 as Active movement against gravity and resistance, 5 as Normal power); NIHSS : National Institutes of Health Stroke Scale; MCA : Middle cerebral artery, PCA : Posterior cerebral artery, ICA : Internal carotid artery; N.R. : Not recorded

Discussions

The study reported an incidence of AIS or TIA after CoronaVac vaccination was 177.3 events per 1,000,000 doses administered. Most of the patients were female, young adult to middle age, and classified as minor stroke (NIHSS <4). The most presenting symptom was hemi-sensory loss. The prognosis was good and most of them had complete recovery (MRS= 0).

The study period was the first phase of CoronaVac distribution to Southern Thailand for healthcare workers such as physicians or nurses who closely contacted with the patients. This was why AIS or TIA were commonly found in young and female gender in our study. Furthermore, atherosclerotic risk factors such as hypertension or diabetes mellitus were found less than 20%. Unlikely study of Lopez-Mena, et al. from Mexico[11], a nationwide study covering abundant vaccine types, the patients with ischemic stroke after CoronaVac immunization were in elderly group and 88% of them had hypertension. In addition, the incidence of 0.43 per 1,000,000 doses administered reported in study of Lopez-Mena, et al. was much lower than that in our study. The discrepancy of incidence may be due to the difference in methodology. Lopez-Mena, et al. included AIS patients who had acute neurological deficit lasting > 24 hours and were confirmed by head CT or MRI. Whereas our study recruited healthcare workers developed AIS or TIA and imaging to exclude other diagnosis. Head CT for diagnosis of AIS within 12 hours of symptoms onset had sensitivity of 0.39[12]. AIS with negative-DWI MRI was reported varied from 7%-29%[13,14] and associated with subsequent stroke or TIA at one year 14%[14]. The strongly characteristics-associated with DWI-negative AIS was posterior circulation ischemia.

Our study showed normal MRI of the brain in 74.3% of patients (29 of 39) with female gender, mild stroke severity and mostly complete recovery. Aben, et al.[15] found that stroke with MRI-negative patients had lower severity at admission, shorter duration of stay and better functional outcome at discharge but less likely diagnosis when compare to stroke with MRI-positive patients. Physicians therefore do not exclude acute stroke based only on MRI-negative.

The most well-known mechanism of COVID-19 vaccine associated ischemic stroke is vaccine-induced immune thrombotic thrombocytopenia (VITT) leading to cerebral venous thrombosis. Laboratory evidence of anti-platelet factor-4 antibody and thrombocytopenia were documented following vaccination with adenoviral vector-based vaccine[7,16]. Thrombosis of intracranial artery is a rare reported condition from ChAdOx1 nCoV-19 in the context of VITT[7]. Whereas inactivated COVID-19 vaccine (BBIBPCorV, Sinopharm) did not affect anti-platelet factor-4, profile of antiphospholipid antibody or clinically increased risk of thrombosis, ChAdOx1 nCoV-19 (adenoviral vector-based vaccine) or BNT162b2 (mRNA vaccine) did not significantly activate fibrinogen-driven coagulation, plasma thrombin generation leading to clinically platelet aggregation[7]. However, Liu J found consistent alteration in hemoglobin A1C, coagulation profiles and renal function after vaccination with inactivated SAR-CoV-2 vaccine[17]. Three of four patients with MRI-positive stroke in our study had atherosclerotic risk factors namely hypertension, diabetes mellitus, hyperlipidemia and old stroke together with moderate to severe narrowing of

intracranial arteries. These implied that CoronaVac might accelerate platelet aggregation or thrombosis in patients with pre-existing intracranial stenosis. We suggest to take precaution when vaccinating people with atherosclerotic risk factors.

Our study reported TIA 41.6% after CoronaVac vaccination which was not easy to establish diagnosis, since TIA is defined by transient stroke symptoms lasting < 24 hours without evidence of infarction by pathology or imaging. Although, DWI-positive MRI was found in 20-60% of TIA who underwent MRI within 3 days[18], it was not available in most medical center.

In Thailand, study from the National Health Security Office's database in 2021 showedthe incidence of acute ischemic stroke in patients aged 15 years or over in Healthy area 12 and 13 (southern part of Thailand) was 335.45 per 100,000 general population (or 3354.5 events per 1 million population)[19]. Apart from this, risk of stroke associated with SAR-CoV-2 (0.8%-1.4%)[11] is much greater than that associated with vaccination. Our study reported incidence of ischemic stroke or TIA after CoronaVac vaccination was 177.3 events per 1,000,000 doses with good functional outcome. This may imply the necessity and acceptable risk of vaccine.

In comparison to other vaccines, Cari L, et al.[8] reported that incidence of AIS in Europe was 65.3, 53.8 and 12.2 events per 1,000,000 administrations of Ad26.COV2-S (Janssen-Johnson & Johnson), ChAdOx1 nCov-19 (AstraZeneca-Oxford), and BNT162b2 (Pfizer-BioNTech) respectively. While Lopez-Mena, et al.[11] reported incidence of AIS in Mexico from CoronaVac, ChAdOx1 nCov-19 and BNT162b2 were 0.43, 0.65 and 0.45 events per 1,000,000 administrations respectively. These explicitly differences were due to methodology as mention earlier. Additionally, the incidence of these study may be underdiagnosed because the reported events were relied on by healthcare providers. Furthermore, some cases in the study of Lopez-Mena occurred in rural settings with limited medical access. Whereas our reported events were diagnosed by neurologists and data was collected from 12 medical centers which widely distributed over Southern Thailand, making it easy to access medical services.

This study had some limitations. First, there were missing data in some centers due to its retrospective nature. Second, although MRI of brain is the best modality to detect acute to subacute ischemic stroke, not all patients with suspected stroke underwent MRI of brain. Forty-two percents of AIS or TIA patients in our study underwent only conventional CT scan (non-contrast axial and coronal plain) which had sensitivity of 0.39 for diagnosis of AIS. However, head CT machine can be adjusted to detect CT "mismatches" by using plain CT (hypodensity), CT angiogram and CT perfusion similar to MRI mismatch[10]. Third, the CoronaVac vaccination related neurological symptoms might be underestimate because of self-limited or mild symptoms. So, the patients did not visit hospital. The strength of this study was the accuracy of the data because clinical and radiographic information were directly assessed by Neurologists and Radiologists. However, physician bias could not be excluded for example, a suspected-stroke patient with uncertain hypodensity on head CT did not undergo MRI to confirm diagnosis.

Conclusion

The incidence of AIS or TIA after CoronaVac vaccination in Southern Thailand was 177.3 events per 1,000,000 doses administered. Most of the patients were female, middle age, and graded as mild severity. The most presenting symptom was hemi-sensory loss. The prognosis was good and most of them had complete recovery as well as the rest of them also had good functional outcome.

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List of names of co-author

1. Pattaranun Luangdilok M.D.,Trang Hospital, Trang, Thailand
2. Pornpong Jitpratoom, Adj. Asst. Prof., Chumphon Khet Udomsakdi Hospital, Chumphon, Thailand
3. Kotchakorn Duangjino, M.D. , Pattani Hospital, Pattani, Thailand
4. Ratchasiri Charoensubsakul, M.D. , Maharaj Nakhon Si Thammarat Hospital, Nakhon Si Thammarat, Thailand
5. Komkrit Panyawattanakit, M.D., Surat Thani Hospital, Surat Thani, Thailand
6. Pharanpong Taemeeyapradit, M.D., Songkhla Hospital, Songkhla, Thailand
7. Wuttipong Vilaivarangkul, M.D., Satun Hospital, Satun, Thailand
8. Tabtim Chongsuvivatwong, M.D., HatYai Hospital, Songkhla, Thailand
9. Suparat Chaisurajinda, M.D., Yala Hospital, Yala, Thailand
10. Thongdaeng Foongyai, M.D., Fort Wachirawut Hospital, Nakhon Si Thammarat, Thailand
11. Umarudee Toamard, M.D., Krabi Hospital, Krabi, Thailand

Adithep Leevattananukool