



# Brain venography performance following the pause of Ad.26.COVID-19 vaccine administration

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## Abstract

Cases of cerebral venous thrombosis (CVT) associated with vaccine induced thrombotic thrombocytopenia (VITT) were reported following administration of the adenoviral vector COVID-19 vaccines, resulting in a pause in Ad.26.COVID-19 vaccine administration in the United States, beginning on April 14, 2021. We aimed to quantify and characterize an anticipated increase in brain venograms performed in response to this pause. Brain venogram cases were retrospectively identified during the three-week period following the vaccine pause and during the same calendar period in 2019. For venograms performed in 2021, we compared COVID vaccinated to unvaccinated patients. There was a 262% increase in venograms performed between 2019 (n = 26) and 2021 (n = 94), compared to only a 19% increase in all radiologic studies. Fifty-seven percent of patients in 2021 had a history of COVID-19 vaccination, with the majority being Ad.26.COVID-19. All patients diagnosed with CVT were unvaccinated. COVID vaccinated patients lacked platelet or D-dimer measurements consistent with VITT. Significantly more vaccinated versus unvaccinated patients had a headache (94% vs 70%, p = 0.0014), but otherwise lacked compelling CVT presentations, such as decreased/altered consciousness (7% vs 23%, p = 0.036), neurologic deficit (28% vs 48%, p = 0.049), and current/recent pregnancy (2% vs 28%, p = 0.0003). We found a dramatic increase in brain venograms performed following publicity of rare COVID-19 vaccine associated CVT cases, with no CVTs identified in vaccinated patients. Clinicians should carefully consider if brain venogram performance is indicated in COVID-19 vaccinated patients lacking thrombocytopenia and D-dimer elevation, especially without other compelling CVT risk factors or symptoms.

**Keywords** Venogram · Ad.26.COVID-19 · COVID-19 · Vaccine · CVT · Thrombosis

## Highlights

- A dramatic increase in venogram performance occurred during the three-week period following the 2021 pause in Ad.26.COVID-19 vaccine administration compared to the same period in 2019.
- The majority of patients undergoing venography had a history of COVID-19 vaccination, most of whom had received the Ad.26.COVID-19 vaccine.
- All patients diagnosed with CVT following the vaccine pause were unvaccinated.
- Only one patient undergoing venography was thrombocytopenic and a small minority of patients had a D-dimer performed, with no patients meeting laboratory criteria for VITT.
- This study suggests that the observed increase in venogram utilization occurred in a population at low risk for

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**Table 1** Comparison of Venogram and All Radiologic Studies Performed during each three-week Study Period

Number of studies by year	2019	2020	2021
Venograms	26	18	94
All Radiologic Studies	98,406	59,094	117,335
Proportions of Venograms	0.026%	0.030%	0.080%
Relative change in studies between years	2019–2020	2020–2021	2019–2021
Venograms	– 31%	422%	262%
All Radiologic Studies	– 40%	99%	19%
Proportions of Venograms	– 15%	163%	203%

The top portion of the table describes the total number of venograms and all radiologic studies for each study period. All radiologic studies include any performed within the 12 hospitals, 7 free-standing emergency departments, and 7 outpatient imaging centers included in this study. The bottom portion of the table describes the relative change in venograms and all radiologic studies between all three study years.

CVT; therefore, in patients recently vaccinated with an adenoviral vector COVID-19 vaccine, in the absence of thrombocytopenia and D-dimer elevation, especially without other compelling CVT risk factors or symptom it may be prudent to reconsider pursuing venography.

## Introduction

In April 2021, several cases of cerebral venous thrombosis (CVT) were reported following administration of the Ad.26.COVID-19 vaccine (Janssen Biotech, Inc., a Janssen Pharmaceutical company, Johnson & Johnson) and ChAdOx1 nCoV-19 vaccine (Oxford/AstraZeneca) [1–3]. As a result, on April 14, 2021, the U.S. Food and Drug Administration (FDA) and U.S. Centers for Disease Control and Prevention (CDC) announced a “pause” in the use of the single-dose Ad.26.COVID-19 vaccine while an investigation was conducted into the rare reports of CVT [4, 5]. As of April 14th, our large healthcare system had administered approximately 18,500 doses of the Ad.26.COVID-19 vaccine, while over 6.8 million doses had been administered throughout the U.S [6]. Because of the widespread attention the rare CVT events received, and because CVT can be challenging to diagnose clinically [7, 8], we sought to quantify and characterize the patients undergoing brain venography to evaluate for CVT in the three weeks immediately following this announcement.

## Methods

To determine the difference in brain venogram utilization following the pause compared to historical cohorts, the total number of venograms performed from April 14 to May 5 in 2019 (pre-pandemic) and 2020 (pandemic) were compared to the same three-week period in 2021. The 2021 cohort

was divided into vaccinated versus unvaccinated patients for comparative analyses. Cases were identified in a retrospective cross-sectional manner based on the inclusion criteria of age 18 and older who had a computed tomography brain venogram (CTV) or magnetic resonance brain venogram (MRV) performed at one of our healthcare system’s 12 hospitals, 7 free-standing emergency departments, and 7 outpatient imaging centers, covering a region with a population of approximately 1.9 million people. Patients less than 18 years of age and any patient with health records not accessible via our electronic medical record (EMR) were excluded from the study. We additionally excluded patients who had a repeat venogram performed to assess progression or resolution of a previously diagnosed CVT. Individual cases were identified by querying the radiology report database (Primordial, Prism, Nuance Communications, Burlington, MA) for our healthcare system. Keyword search of the radiology reports was employed using the following keywords: venogram, venography, CTV, MRV, venous sinus thrombosis, venous sinus thrombus. Data abstracted from our EMR included patient demographics, CVT symptoms, CVT risk factors, comorbidities, radiologic evaluation, and additional non-imaging diagnostic workup. Vaccination status was verified by accessing an enterprise data warehouse, which facilitated capturing the vaccination record for patients vaccinated outside our healthcare system. We analyzed data with standard statistical methods utilizing the SAS program version 9.4 (SAS, Cary, NC, USA). Descriptive statistics are reported as means with corresponding standard deviations for continuous variables and percentages for categorical variables. Univariate analysis was performed to compare the vaccinated versus unvaccinated cohorts. Categorical variables were evaluated using Pearson’s chi-squared and Fisher’s exact test where appropriate. Continuous and ordinal variables were evaluated using Wilcoxon two-sample tests. Statistical significance was set at  $p \leq 0.05$ , and all reported  $p$  values are two-tailed.

**Table 2** Comparison Based on Vaccination Status for Patients with Brain Venograms Performed

Variable	2021 COVID-19 Vaccination		p-value
	No (n=40)	Yes (n=54)	
<b>Demographics</b>			
Age, mean $\pm$ SD	40.2 $\pm$ 16.6	43.3 $\pm$ 12.5	0.147
Female Sex	31 (77.5)	48 (88.9)	0.136
<b>Race</b>			
White or Caucasian	23 (57.5)	33 (61.1)	0.242
Black or African American	12 (30.0)	18 (33.3)	
Asian	1 (2.5)	1 (1.9)	
American Indian or Alaska native	0 (0.0)	0 (0.0)	
Hispanic or Latino	0 (0.0)	2 (3.6)	
Middle Eastern or North African	2 (5.0)	0 (0.0)	
Not specified	2 (5.0)	0 (0.0)	
<b>Ethnicity</b>			
Hispanic or Latino	1 (2.5)	3 (5.6)	0.625
Non-Hispanic or Latino	38 (95.0)	48 (88.9)	
Not specified	1 (2.5)	3 (5.6)	
BMI, mean $\pm$ SD	32.0 $\pm$ 8.4	31.4 $\pm$ 9.2	0.701
<b>Symptoms</b>			
Headache	28 (70.0)	51 (94.4)	0.001
Decreased/Altered Consciousness	9 (22.5)	4 (7.4)	0.036
Neck Pain	3 (7.9)	0 (0.0)	0.085
Neurologic Deficit	19 (47.5)	15 (27.8)	0.049
Seizure	3 (7.7)	0 (0.0)	0.070
Vomiting	6 (15.0)	3 (5.6)	0.163
<b>Prothrombotic Risk Factors and Other Comorbidities</b>			
Current or recent pregnancy	11 (27.5)	1 (1.8)	0.0003
Prothrombotic Condition	3 (7.5)	4 (7.5)	1.000
Migraine history	9 (22.5)	12 (22.2)	0.975
Head trauma within the previous month	5 (12.5)	1 (1.8)	0.080
Neurosurgery within the previous month	3 (7.7)	0 (0.0)	0.070
Hospitalization within the previous month	9 (22.5)	1 (1.8)	0.002
CNS/Ear infection	2 (5.0)	1 (1.8)	0.571
CNS Malignancy	0 (0.0)	0 (0.0)	–
Malignancy other	0 (0.0)	1 (1.8)	1.000
OCP Use/Hormone Replacement Therapy	3 (7.7)	8 (14.8)	0.348
Current Smoking	9 (22.5)	9 (16.7)	0.477
Previous CVT	2 (5.0)	0 (0.0)	0.178
<b>Imaging and Diagnostic Studies Performed</b>			
CVT on imaging	2 (5.0)	0 (0.0)	0.178
Platelet count performed	35 (87.5)	45 (83.3)	0.575
Platelet count, Mean $\pm$ SD	265.0 $\pm$ 73.0	262.1 $\pm$ 76.0	0.779
D-dimer performed	1 (2.5)	3 (5.6)	0.364

The number of cases per year identified for each categorical variable are represented with the percentage of total cases for that year, n (%)

SD standard deviation, BMI body mass index, CNS central nervous system, OCP oral contraceptive pill, CVT cerebral venous thrombosis

<sup>a</sup>Prespecified as previous deep venous thrombosis or pulmonary embolism, Deficiencies of protein C, protein S, antithrombin III, plasminogen, activated protein C resistance/factor V Leiden mutation, anticardiolipin antibodies, lupus anticoagulant

## Results

There was a 262% increase in the number of venograms performed when comparing the same three-week period from 2021 (n = 94) following the vaccine pause to 2019 (n = 26). In contrast, there were 117,335 radiologic studies performed during the 3-week period in 2021, versus 98,406 in 2019, representing only a 19% increase in all radiologic studies performed. Additional relative changes of venograms and all radiologic studies performed in 2019, 2020, and 2021 are listed in Table 1. For patients undergoing venography in 2021, 56% (n = 53/94) of venograms were performed in the ED, 32% (n = 30/94) were performed as an inpatient, and 12% (n = 11/94) were ordered as outpatient studies. Fifty-seven percent (n = 54) of patients had a history of COVID-19 vaccination, with the majority being Ad.26.COV2.S vaccinations. A comparison of COVID-19 vaccinated versus unvaccinated patients undergoing venography in our three-week study period is provided in Table 2. Significantly more vaccinated versus unvaccinated patients had a headache (94% vs 70%,  $p = 0.001$ ), but otherwise lacked compelling presentations for CVT, such as decreased/alterd consciousness (7% vs 23%,  $p = 0.036$ ), neurologic deficit (28% vs 48%,  $p = 0.049$ ), and current/recent pregnancy (2% vs 28%,  $p = 0.0003$ ). No COVID-19 vaccinated patients were diagnosed with a CVT, versus 5% (n = 2) in the unvaccinated group. Of COVID-19 vaccinated patients undergoing venography, 83% (n = 45) had a platelet count performed, of whom only one had thrombocytopenia, defined as  $< 150 \times 10^9/L$ . Additionally, only 5.6% (n = 3) of patients had a D-dimer performed, with no values markedly elevated and consistent with VITT ( $> 4$  times upper limit of normal).

## Discussion

Our data suggest that during the same three-week period in 2019, 2020, and 2021 that trends in venogram utilization likely resulted from the reported rare risk of CVT associated with COVID-19 vaccination, and not from the risk of CVT associated with COVID infection. Moreover, the increased venogram utilization in vaccinated patients appears to have been in a population at overall low risk for CVT, because they lacked compelling symptoms for CVT (beyond headache), lacked prothrombotic risk factors or other comorbidities predisposing to CVT, and lacked laboratory findings consistent with VITT. Given the dramatic increase we found in venograms performed within just one healthcare system that was associated with the extensive publicity of

rare CVT cases in the setting of VITT, it is likely venogram utilization increased in other settings as well. Moving forward, clinicians should carefully consider if performance of a venogram is indicated in adenoviral vector COVID-19 vaccinated individuals, in the absence of thrombocytopenia and D-dimer elevation, especially without other compelling CVT risk factors or symptoms.

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**Data availability** Data available within the article or its supplementary material.

**Code availability** Not applicable.

## Declarations

**Conflict of interest** None.

**Ethical approval** Electronic medical record access approved by institutional review board.

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