

Cerebral venous thrombosis after ChAdOx1 nCoV-19 vaccination: a systematic review

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Abstract. – OBJECTIVE: To perform a systematic review of case reports or case series regarding thrombosis with thrombocytopenia syndrome (TTS) and cerebral venous thrombosis (CVT) related to ChAdOx1 nCoV-19 vaccination to address the clinical features, laboratory findings, treatment modalities, and prognosis related with CVT.

SUBJECTS AND METHODS: We included 64 TTS patients from 19 articles, 6 case series and 13 case reports, in which thrombosis occurred after the first dose of ChAdOx1 nCoV-19 vaccination published up to 30 June 2021 in Embase, ePubs, Medline/PubMed, Scopus, and Web of Science databases.

RESULTS: Of the 64 TTS patients, 38 (59.3%) had CVT. Patients with CVT were younger (me-

dian 36.5 vs. 52.5 years, $p<0.001$), had lower fibrinogen levels (130 vs. 245 mg/dL, $p=0.008$), had more frequent history of intracerebral hemorrhage (ICH), and had higher mortality rate (48.6% vs. 19.2%, $p=0.020$) than that of patients without CVT. In multivariable analysis, the possibility of presence of CVT was higher in younger age groups [odds ratio (OR): 0.91, 95% confidence interval (CI): (0.86-0.97, $p<0.001$)] and those with accompanying intracerebral hemorrhage (ICH) (OR: 13.60, 95% CI (1.28-144.12, $p=0.045$).

CONCLUSIONS: Our study demonstrated that CVT related to ChAdOx1 nCoV-19 vaccination was associated with younger age, low levels of fibrinogen, presence of ICH and more frequent mortality compared to those of non-

CVT. If TTS occurs after ChAdOx1 nCoV-19 vaccination, the presence of CVT in patients with young age or ICH should be considered.

Key Words:

Cerebral venous thrombosis, COVID-19, ChAdOx1 nCoV-19 vaccine, Thrombosis with thrombocytopenia syndrome, Intracerebral hemorrhage, Prognosis.

Introduction

COVID-19 vaccinations have been rapidly implemented around the world¹. Current COVID-19 vaccines include mRNA vaccines [mRNA-173 (Moderna) and BNT162b2 (Pfizer-BioNTech)] and adenovirus vector vaccines [ChAdOx1 nCoV-19 (AstraZeneca) and Ad26.COV2.S (Johnson & Johnson/Janssen)]². Although these vaccines are effective against COVID-19 infection *via* neutralizing antibody formation, several side effects associated with COVID-19 vaccination have been reported, particularly in ChAdOx1 nCoV-19 vaccine³. ChAdOx1 nCoV-19 vaccine can cause thrombosis and thrombocytopenia through a mechanism related to pathologic antibodies to platelet factor 4, and this pathologic condition can lead to systemic venous thrombosis⁴.

Cerebral venous thrombosis (CVT) is defined as the presence of a blood clot in the cerebral veins or dural venous sinuses. CVT is accompanied by headaches, stroke-related symptoms, and seizures⁵. Hematologic disorders, inflammatory diseases, pregnancy, hormonal abnormality, and meningitis are the main associations or risk factors for the development of CVT⁵. Since the initiation of COVID-19 vaccination, reports of cases of CVT associated with COVID-19 have been reported⁶. In particular, the occurrence of CVT is associated with ChAdOx1 nCoV-19 vaccination, and in some cases, fatal CVT may occur^{7,8}. Because the CVT itself is a rare disease, case reports or case series are essential to understand the characteristics and associated factors of thrombosis with thrombocytopenia syndrome (TTS) associated with ChAdOx1 nCoV-19 vaccination, especially CVT. Moreover, in a recent study⁹, we suggested that CVT was one of the important factors in mortality associated with ChAdOx1 nCoV-19 vaccination. Our previous work⁹⁻¹¹ discussed vaccine-induced immune thrombotic thrombocytopenia (VITT)-related complications, but CVT *vs.* non-CVT has not been analyzed. In this study, we aimed to undertake a systematic re-

view to investigate published case reports or case series regarding CVT for addressing the clinical and laboratory findings, treatment modalities, and prognosis related to CVT.

Subjects and Methods

Search Strategy and Data Collection

This study was conducted according to the PRISMA statement¹². TTS cases associated with published ChAdOx1 nCoV-19 vaccination were reviewed and among them, cases described for CVT and cases without CVT were compared. After reviewing individual abstracts and full texts, we further excluded non-English articles, abstracts, letters to the editors, review articles, articles that did not contain sufficient information on the patients, and duplicate cases. Three reviewers (S.B. Lee, S.H. Park, and J.I. Shin) independently examined the studies, and any disagreement among the authors was resolved by consensus. Finally, a total of 19 articles, 6 case series and 13 case reports, in which thrombosis occurred after the first dose of ChAdOx1 nCoV-19 vaccination were included in this systematic review of case series (Figure 1)^{7,8,13-21}. We identified demographic, clinical, laboratory findings, immunologic and platelet activation assays, thrombosis, hemorrhage, treatment modalities, the weight of association factors for venous thrombosis (4T score)²², and mortality from these included articles.

Statistical Analysis

Categorical variables were compared using Fisher's exact and continuous variables were compared with the Mann-Whitney U-test. Multivariable logistic regression analyses with backward elimination were performed to investigate association factors for the presence of CVT after adjusting variables with a *p*-value less than 0.1 in univariable analysis [age, fibrinogen, platelet count (less than $25 \times 10^3/\mu\text{L}$), presence of intracerebral hemorrhage (ICH)]. Statistical analyses were performed by R version 4.0.4 (R Core Team, Vienna, Austria). In all statistical analyses, a two-tailed *p*-value <0.05 was considered significant²³.

Results

Countries that reported CVT varied, and the day of symptom onset was between 2 and 24 days after vaccination. Among 19 articles and

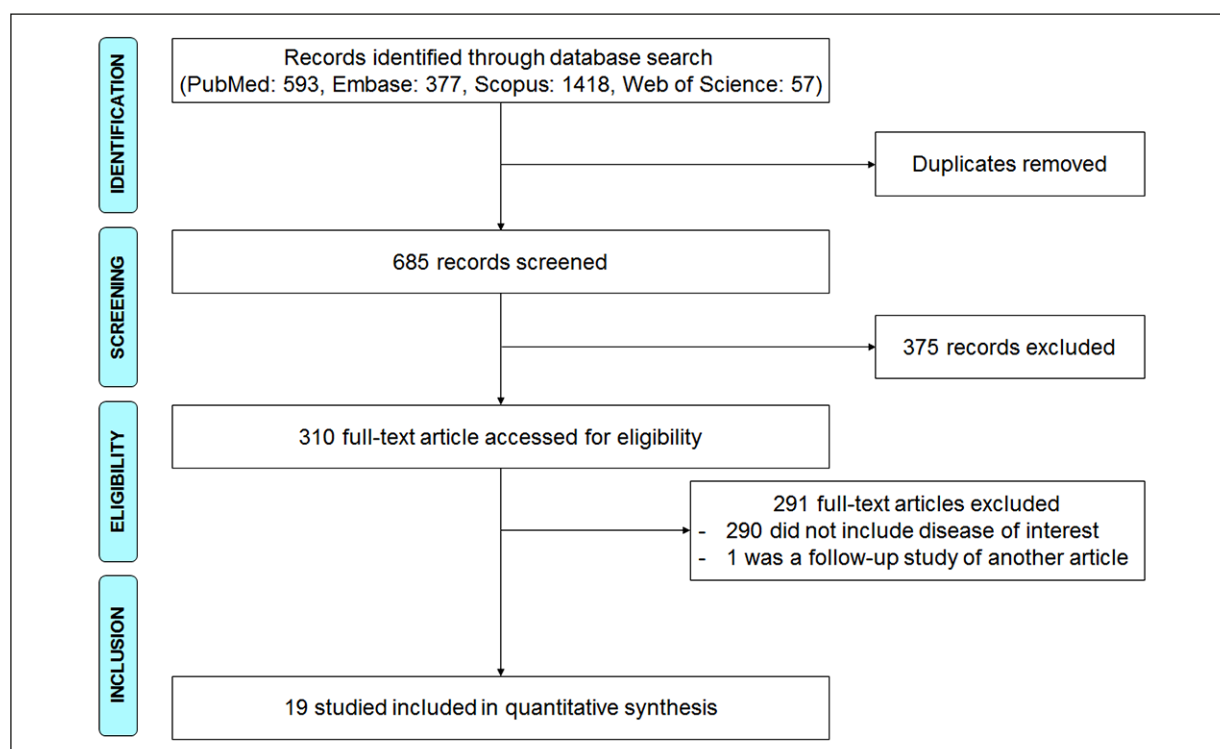


Figure 1. Flow chart showing the selection process of studies.

64 TTS patients, 38 (59.3%) had CVT. The median age of patients with CVT was 36.5 years and 73.3% were female. Detailed main clinical presentation, laboratory findings, presence of thrombosis/hemorrhage, treatment modalities, and presence of mortality were described in Table I. Patients with CVT were younger (median 36.5 vs. 52.5, $p < 0.001$) and had lower fibrinogen levels (130 vs. 245 mg/dL, $p = 0.008$) than those without CVT. The proportion of fibrinogen levels with less than 200 mg/dL was greater in patients with CVT compared to those without CVT (73.3% vs. 40.0%, $p = 0.038$). Mortality was more frequently noted in patients with CVT compared to those without CVT (48.6% vs. 19.2%, $p = 0.020$). In contrast, the results of the anti-platelet factor 4/heparin antibody enzyme-linked immunosorbent assay and functional heparin-induced thrombocytopenia assay were not different according to the presence or absence of CVT.

Considering characteristics of accompanying thrombosis and hemorrhage, the frequency of multiple systemic venous thromboses was not different according to the presence of CVT.

Moreover, frequency of thrombosis site (brain, heart, lung, and gastrointestinal system), size of involved vessels (deep vein, aorta, aortoiliac, jugular vein, and inferior vena cava), and hemorrhage sites (intracerebral hemorrhage, subarachnoid hemorrhage, and adrenal hemorrhage) were also not different regardless of the presence of CVT.

Regarding treatment modality for CVT, the frequency of use of fondaparinux (4.3% vs. 31.3%, $p = 0.033$), intravenous immunoglobulin (28.0% vs. 68.8%, $p = 0.022$), non-heparin anticoagulants (20.0% vs. 56.3%, $p = 0.023$), and direct thrombin inhibitor (4.0% vs. 37.5%, $p = 0.009$) were lower in patients with CVT compared to patients without CVT (Table I).

Considering the association factors for CVT, the 4T scores were not different between CVT and non-CVT patients. On the contrary, the possibility of presence of CVT was higher in younger age groups [odds ratio (OR): 0.91, 95% confidence interval (CI) (0.86 - 0.97), $p < 0.001$] and those with accompanying intracerebral hemorrhage [OR: 13.60, 95% CI (1.28 - 144.12) $p = 0.045$] in multivariable analysis. Regarding the mortality

Table I. RComparative analyses of demographic, clinical, laboratory findings, thrombosis, hemorrhage, and treatment in patients with venous thrombosis with thrombocytopenia after ChAdOx1 nCoV-19 vaccination.

Variables	Total patients (n = 64)	Non-CVT* (n = 26)	CVT (n = 38)	p-value
	Number of patients (%) or Median (IQR)	Number of patients (%) or Median (IQR)	Number of patients (%) or Median (IQR)	
Demographics				
Age	44.5 (34.37, 58.00)	52.50 (39.50, 67.75)	36.50 (29.25, 48.25)	< 0.001
Age ≤ 60 years†	54/64 (84.4%)	17/26 (65.4%)	37/38 (97.4%)	0.001
Female	37/54 (68.5%)	15/24 (62.5%)	22/30 (73.3%)	0.556
Time to presentation‡	9.75 (7.50, 12.75)	9.50 (7.00, 12.50)	10.00 (8.00, 13.00)	0.559
Clinical presentations				
Systemic	15/30 (50.0%)	6/14 (42.9%)	9/16 (56.3%)	0.715
Neurologic	26/30 (86.7%)	10/14 (71.4%)	16/16 (100.0%)	0.037
Bleeding	3/30 (10.0%)	1/14 (7.1%)	2/16 (12.5%)	1.000
Gastrointestinal	7/30 (23.3%)	2/14 (14.3%)	5/16 (31.3%)	0.399
Cardiopulmonary	4/30 (13.3%)	4/14 (28.6%)	0/16 (0.0%)	0.037
Laboratory findings				
Platelet count (cells/mm ³)	36,000 (21,000, 71,000)	44,000 (26,250, 70,750)	28,000 (15,750, 71,250)	0.245
Platelet < 25 × 10 ³ /μL	22/62 (35.4%)	5/24 (20.8%)	17/38 (44.7%)	0.064
Fibrinogen (mg/dL)	187.50 (100.00, 317.5)	245.00 (120.00, 425.00)	130.00 (80.00, 210.00)	0.008
Fibrinogen < 200 mg/dL	30/50 (60.0%)	8/20 (40.0%)	22/30 (73.3%)	0.038
D-dimer/Upper limit of normal range	58.85 (21.03, 75.27)	53.40 (21.62, 80.45)	64.30 (20.45, 70.10)	0.684
HIT ELISA (OD)	2.02 (1.02, 2.94)	1.79 (0.90, 2.83)	2.26 (1.14, 3.06)	0.379
Platelet activation assay	19/21 (90.4%)	6/7 (85.7%)	13/14 (92.9%)	1.000
Thrombosis and Hemorrhage				
Presence of any site of hemorrhage	21/64 (33.8%)	6/26 (23.1%)	15/38 (39.5%)	0.189
ICH (intracerebral hemorrhage)	12/64 (19.3%)	2/26 (7.7%)	10/38 (26.3%)	0.062
Treatment				
Heparins	26/39 (66.6%)	9/16 (56.3%)	17/23 (73.9%)	0.312
Fondaparinux	6/39 (15.3%)	5/16 (31.3%)	1/23 (4.3%)	0.033
Steroids	13/41 (31.7%)	7/16 (43.8%)	6/25 (24.0%)	0.302
Intravenous immunoglobulin	18/41 (43.9%)	11/16 (68.8%)	7/25 (28.0%)	0.022
Neurosurgery	8/41 (19.5%)	1/16 (6.3%)	7/25 (28.0%)	0.120
Non-heparin anticoagulants	14/41 (34.1%)	9/16 (56.3%)	5/25 (20.0%)	0.023
Direct thrombin inhibitor	7/41 (17.0%)	6/16 (37.5%)	1/25 (4.0%)	0.009
4T Score	6.25 (6.00, 7.00)	6.50 (6.00, 7.00)	6.00 (6.00, 7.00)	0.744
Mortality	23/63 (36.5%)	5/26 (19.2%)	18/37 (48.6%)	0.020

Data are presented as median (interquartile range) or number (percent). *Cerebral venous thrombosis. †10 patients with age range 22-49 were classified as age at or less than 60, when exact age was not accessible. IQR: interquartile range. HIT ELISA (OD): heparin-induced thrombocytopenia enzyme-linked immunosorbent assay (optical density). ICH: intracerebral hemorrhage. ‡If time to admission after vaccination was not given, time to symptom onset after vaccination was used.

according to the treatment modality, there was no difference, i.e., fondaparinux, intravenous immunoglobulin, non-heparin anticoagulants, and direct thrombin inhibitor, in both CVT and non-CVT patients.

Discussion

Our study demonstrates information on the clinical, laboratory characteristics, prognosis, treatment modality, and association factors of CVT which occurred after ChAdOx1 nCoV-19 vaccination. In our study, patients with CVT were younger and had lower fibrinogen levels than those without CVT. Our results support those of previous research and reports²⁴⁻²⁷ of European Medicines Agency presentations which demonstrated that an adverse immune reaction called immunosenescence may occur in young people and also this abnormal immune reaction led to disseminated intravascular coagulation-like blood changes after ChAdOx1 nCoV-19 vaccination. Although our study was unable to provide a definitive cut-off value for age and fibrinogen levels, it suggested that in patients with TTS accompanying young age or low fibrinogen levels, it may be necessary to consider the possibility of accompanying related CVT.

Our study demonstrated that patients with TTS accompanying CVT after ChAdOx1 nCoV-19 vaccination were associated with poor prognosis, particularly mortality. In CVT, brain edema and ICH are often accompanied, which can lead to an increase of intracranial pressure, transtentorial herniation, and a high mortality rate^{28,29}. Furthermore, in our study, the presence of ICH was independently associated with the presence of CVT patients who received ChAdOx1 nCoV-19 vaccination. Although one-third of ICH is accompanied by CVT, in real clinical practice, it is not easy to determine whether CVT is accompanied or not because the status of the ICH varies²⁷. Since the likelihood of ICH may be increased due to vaccination-related heparin-induced thrombocytopenia³⁰, it is essential to consider the presence or absence of CVT when ICH is noted in ChAdOx1 nCoV-19 vaccinated individuals. Further study regarding the association of ICH with CVT after ChAdOx1 nCoV-19 vaccination is required.

In our study, CVT patients were less likely to receive anticoagulant treatment. This trend may be because coagulopathy induced by vaccina-

tion was more commonly associated with CVT. In principle, anticoagulant therapy should be administered even if the intracerebral hemorrhage is present in CVT³¹. However, no such trend was observed in our dataset. This may be because the administration of anticoagulants was difficult due to brain edema or other unknown causes. However, in our published cases-based systematic review, detailed validation of brain image findings and brain edema is difficult, therefore, additional research considering these aspects is needed.

Limitations

Findings from the present study should be interpreted in light of its limitations. First, it was difficult to investigate independent factors for CVT and CVT-related mortality because of the small sample size. Second, there is a possibility that there is a publication bias, since only serious or unusual case series may be published. Third, because our study was a retrospective observational study, it is difficult to present a causal relationship. Finally, laboratory findings and clinical features of our study such as thrombosis or the location of hemorrhage may reflect post-vaccination status rather than underlying causes.

Conclusions

Our study demonstrates that CVT related to ChAdOx1 nCoV-19 vaccination was associated with younger age, low levels of fibrinogen, and more frequent mortality rather than those of non-CVT. In patients with TTS related to ChAdOx1 nCoV-19 vaccination, younger age and accompanying ICH were related to CVT. Therefore, in the case of TTS related to ChAdOx1 nCoV-19 vaccination, there is a possibility of poor prognosis when accompanied by CVT, and a possibility of CVT when accompanied by ICH.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Availability of Data and Materials

Our data is a systematic review of online published articles, which can be obtained by using our search terms online. Our manuscript dataset can be obtained from the corresponding authors upon appropriate request.

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