Review Article

ISSN: 1735-0344 *Tanaffos 2022; 21(4): 413-418*

TANAFFOS

COVID-19 and Vaccine-Induced Thrombosis

Babak Sharif-Kashani [1,2], Shadi Shafaghi [2], Farah Naghashzadeh [2], Abdolreza Mohamadnia [3], Mohammad Rahdar [2], Maryam Hajimoradi [2], Sima Noorali [2]

[1] Tobacco Prevention and Control Research Center(TPCRC), National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran, [2] Lung Transplantation Research Center, NRITLD, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [3] Chronic Respiratory Disease Research Center, NRITLD, Shahid Beheshti University of Medical Science, Tehran, Iran

Received: 16 November 2021
Accepted: 6 July 2022

Correspondence to: Noorali S
Address: Lung Transplantation Research Center, NRITLD, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Email address: simanoorali@yahoo.com

Coronavirus disease 2019 (COVID-19), a highly contagious infectious disease, has had a catastrophic effect on the world's demographics resulting in more than 2.9 million deaths worldwide till January 2021. It can lead to systemic multi-organ complications; in particular, venous and arterial thromboembolism risk is significantly increased. Venous thromboembolism (VTE) occurs in 22.7% of patients with COVID-19 in the ICU and 8% in non-ICU hospitalized patients. Studies evaluating thromboprophylaxis strategies in patients with COVID-19 are needed to improve the prevention of VTE. VTE is the most commonly reported thrombotic complication, with higher incidence rates among critically ill patients. Several vaccines have been licensed and are currently used to combat the COVID-19 pandemic. Also, several cases of vaccine-induced thrombosis have been reported. Vaccination remains the most critical measure to curb the COVID-19 pandemic. There is a broad consensus that the benefits of vaccination greatly outweigh the potential risks of rare vaccine side effects, such as vaccine-induced immune thrombotic thrombocytopenia (VITT). Therefore, the importance of vaccination should be emphasized. This statement aims to focus on VITT.

Keywords: COVID-19; Vaccine; Vaccine-Induced Thrombosis; VITT; SARS-CoV-2

INTRODUCTION

Coronavirus disease 2019 (COVID-19), a highly contagious infectious disease, has had a catastrophic effect on the world's demographics resulting in more than 2.9 million deaths worldwide till January 2021 (1,2). It can lead to systemic multi-organ complications; in particular, the risk of both venous and arterial thromboembolism is significantly increased (3-6). Venous thrombosis, comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), occurs with an incidence of approximately one per 1000 annually in general populations (7). Venous thromboembolism (VTE) occurs in 22.7% of patients with COVID-19 in the ICU and 8% in non-ICU hospitalized patients. Studies evaluating thromboprophylaxis strategies in patients with COVID-19 are needed to improve the prevention of VTE (6). VTE is the most commonly reported thrombotic complication, with higher incidence rates among critically ill patients (8).

Several vaccines have been licensed and are currently used to combat the COVID-19 pandemic. Several cases have been reported to the European Medicines Agency, including at least 169 possible cases of cerebral venous sinus thrombosis and 53 possible cases of splanchnic vein thrombosis among 34 million recipients of the ChAdOx1 nCoV-19 (Astrazeneca) vaccine, 35 possible cases of central nervous system thrombosis associated with low blood platelets, among 54 million recipients of the BNT162b2 (Pfizer–BioNTech mRNA) vaccine, and five possible (but

unvetted) cases of cerebral venous sinus thrombosis among four million recipients of the mRNA-1273 (Moderna mRNA) vaccine (9). Six possible cases of cerebral venous sinus thrombosis have been reported among the more than seven million recipients of the Ad26.COV2.S adenoviral vector (Johnson & Johnson/Janssen) vaccine. It must be emphasized that all these case reports have not been subjected to rigorous central review, and these numbers may be underestimated because reporting is voluntary. Nevertheless, they indicate the need for maintaining a high level of concern when patients present with central nervous system or abdominal symptoms after receiving any SARS-CoV-2 vaccine (9).

Greinacher et al. wrote that the thrombosis mechanism resembles severe heparin-induced thrombocytopenia (HIT) after ChAdOx1 nCov-19 vaccination, but unlike the usual situation, none of these patients were exposed to heparin during the previous days. They concluded that the vaccines can result in a rare syndrome that clinically mimics autoimmune heparin-induced thrombocytopenia (aHIT), and proposed using the term vaccine-induced immune thrombotic thrombocytopenia (VITT) for the first time to avoid confusion. A past publication about ChAdOx1 nCov-19 vaccination referred to this syndrome as vaccine-induced prothrombotic immune thrombocytopenia (VIPIT). These blood clots were found to occur in approximately one in 100,000 people who received the vaccine (10). This statement aims to focus on vaccine-induced thrombosis.

Thrombosis prevalence and incidence after the first or second dose of the COVID-19 vaccine

VTE prevalence in COVID-19 patients in the ICU and non-ICU hospitalized patients is 22.7% and 8%, respectively (6). The UK's Medicines and Healthcare Products Regulatory Agency received 79 reports of thrombosis associated with low platelets by 31 March, of which 44 cases were cerebral venous sinus thrombosis (CVST). Of these 79 cases, 51 (13 fatal) were in women, and 28 (six fatal) were in men. So far, all UK cases have occurred after the first dose (9).

In 513284 patients with a COVID-19 diagnosis, the incidence of cerebral venous thrombosis was 39.0 per million people, and in 489871 patients who had received COVID-19 vaccination, the incidence was 4.1 per million (1.1 to 14.9 million) (11).

Mortality rate after vaccination-induced thrombosis

Based on a CDC report, more than 324 million doses of COVID-19 vaccines were administered in the United States from December 14, 2020, to June 28, 2021. During this time, Vaccine Adverse Event Reporting System (VAERS) received 5,718 reports of death (0.0018%) among COVID-19-vaccinated people. FDA requires healthcare providers to report any death after the COVID-19 vaccination to VAERS, even if it is unclear whether the vaccine was the cause or not. Reports of adverse events following vaccination, including deaths, do not necessarily mean that a vaccine caused a health problem. A review of available clinical data, including death certificates, autopsy, and medical records, has not established a causal link to COVID-19 vaccines. However, recent reports have indicated a possible causal relationship between the J&J/Janssen COVID-19 vaccine and TTS, a rare and serious adverse event that causes blood clots with low platelets leading to death (12).

Vaccination-induced thrombosis signs and symptoms

The symptoms likely begin five to ten days post-vaccination, leading to the identification of cases typically between 5 to 30 days post-vaccination. If there is a delay in recognizing the symptoms and/or in seeking medical attention, the identification can be later. Symptoms of thrombosis include severe unremitting headache, backache, abdominal pain, and chest pain.

A disseminated intravascular coagulation (DIC)-like picture can happen in VITT and although bleeding predominates in acute DIC, thrombosis predominates in

VITT. However, bleeding complications, especially intracerebral bleeding, have been reported in VITT.

Isolated thrombocytopenia (without thrombosis) with hemorrhage has also been reported. Thrombocytopenia may be suspected based on the presence of petechiae or minor bleeding (bruising) (12).

Locations of thrombosis

Often thrombi are present at multiple sites, frequently with thrombosis in unusual locations.

Venous

•Cerebral venous thrombosis, also called cerebral venous sinus thrombosis, may present as intracerebral hemorrhage.

•Splanchnic vein thrombosis includes mesenteric, portal, splenic, and hepatic veins.

•Adrenal vein thrombosis may present as adrenal hemorrhage; if bilateral, the patient is at risk for acute adrenal failure.

•Pulmonary embolism is more common than DVT.

•In a series of 22 individuals with VITT, 13 cases (60 percent) had CVT. Other unusual sites of thrombosis, such as the ophthalmic vein, have also been reported (13).

Arterial

•Ischemic stroke, especially middle cerebral artery territory

•Acute limb ischemia

•Sudden death (diagnosis of VITT established post-mortem) may reflect any number of thrombotic complications, including coronary thrombosis, pulmonary embolism, or intracerebral hemorrhage (12).

Lab data suggesting post-vaccination thrombosis

Individuals with VITT have a high frequency of overt, decompensated DIC, which manifests the following abnormalities:

●Moderate to severe thrombocytopenia (normal platelet count in adults ranging from 150,000 to 450,000 platelets per microliter of blood)

●Elevated D-dimer (the reference concentration of D-dimer is < 250 ng/ml)

Elevations in D-dimer are very nonspecific and may reflect ongoing thrombosis, chronic inflammatory states, and/or DIC (12).

●Decreased fibrinogen (approximately half have a fibrinogen level below the normal range; many of the remainders are in the low-normal range)

●Normal or mildly increased prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT)

Risk factors of vaccination-induced thrombosis

Risk factors for VITT are unknown. Female sex and younger age were proposed as possible risk factors based on initial reports:

Initial reports suggested a female predominance. However, this may reflect the demographics of the first wave of individuals (young female healthcare workers) to receive the vaccine (10,14). In a series from the United Kingdom, 14 out of 23 cases (61 percent) were female (13). In the first three cases from Canada, two were males, and all were over the age of 60 years; this was during the period when the ChAdOx1 nCoV-19 vaccine was being avoided in younger women (15).

Initial reports suggested that individuals with VITT were younger (<55 or 60 years). One study has highlighted three independent descriptions of 39 cases with a newly described syndrome characterized by thrombosis and thrombocytopenia. They were healthy, and very few had previous thrombosis or a preexisting prothrombotic condition. Most of them included were women younger than 50 years of age, some of whom were receiving estrogen replacement therapy or oral contraceptives (9). The combined oral contraceptive pill also increases the risk of blood clots, and these clots are likely formed by a different mechanism (16).

Certain European Union countries have restricted the use of vector vaccines by older age groups and recommended that the AstraZeneca vaccine should

preferably not be given to people under 30 years. Individuals who have received the first dose already may be receiving a different vaccine for the second dose, but there is no available data on the efficacy of this approach (17).

Prophylaxis of vaccine-induced thrombosis

Routine pharmacological thromboprophylaxis with anticoagulants or antiplatelet agents to prevent atypically located thrombosis resulting from the specific immunological response following vaccination is not indicated (18). Especially, there is no role for taking aspirin before or following vaccination as a strategy to reduce the risk of VITT(12).

COVID-19 vaccine injection in people with a history of thrombosis or hypercoagulable state

Due to the immunogenetics of thrombosis, patients with a positive history of thrombosis do not have an increased risk of developing this specific and very rare complication after vaccination (19).

Also, having a blood-clotting tendency, such as Factor V Leiden, may put the patient at higher risk of blood clots, but the vaccine does not increase this. People who have COVID-19 are at higher risk of developing blood clots. Therefore, because COVID-19 often causes blood clots, the vaccine will provide patients with protection against developing another blood clot (19).

COVID-19 vaccine injection in people using blood thinners (ASA, Warfarin, Clopidogrel, and NOAC)

Individuals taking novel oral anticoagulants (NOACs), such as apixaban, dabigatran, edoxaban, and rivaroxaban, warfarin in therapeutic INR range, full-dose heparin, or fondaparinux injections, for any indications, can all receive the COVID-19 vaccination. Vaccinating before the next dose of anticoagulant may be considered rather than immediately after taking the blood thinner. There is a risk of bruising at the injection site, but serious effects are not anticipated. Prolonged pressure (for at least 5 minutes) should be applied to the injection site; patients on warfarin with supra-therapeutic INR should wait until their INR is <4.0 (18,20).

Management of vaccine-induced thrombosis

Consulting a hematologist or other hemostasis and thrombosis expert is critical to assist with the evaluation and management of VITT. Many individuals are hospitalized due to the severity of their clinical condition, except individuals with isolated thrombocytopenia who can be treated with a NOAC with very close follow-up(21).

Anticoagulation

Therapeutic anticoagulation is one of the primary treatments for VITT and is used unless there is a contraindication, such as expanding intracerebral hemorrhage.

In addition to patients with confirmed VITT-associated thrombosis, therapeutic anticoagulation is also indicated in individuals with a strong clinical suspicion for VITT who are awaiting confirmatory testing and those with positive laboratory testing for VITT who have not had a thrombosis (12).

Early reports, in which VITT patients were treated with heparins described clinical worsening, including death, although it is unknown whether heparin exposure contributed to poor outcomes. Because of the similarity between HIT and aHIT, most experts caring for the initial patients suggest using a non-heparin anticoagulant (12).

The choice of non-heparin anticoagulant depends on the patient's clinical status based on the risk of bleeding, the need for an invasive procedure, and/or the anticipated need to stop anticoagulation. In individuals who can take oral medications, anticoagulants in order of preference are:

- NOACs include factor Xa inhibitors (apixaban, edoxaban, or rivaroxaban); the oral direct thrombin inhibitor dabigatran may also be an option, although it is less studied.
- Fondaparinux or danaparoid
- A parenteral direct thrombin inhibitor (argatroban or bivalirudin).

Standard full-therapeutic dosing is appropriate, provided that there is no active bleeding, with appropriate adjustments for body weight and kidney function.

The appropriate duration of anticoagulation is unknown. Analogous to spontaneous HIT following orthopedic surgery, thrombocytopenia can be prolonged. A reasonable approach for VITT with thrombosis would be to continue anticoagulation for three months after normalization of the platelet count, as long as no further thrombosis occurs. For VITT without thrombosis, anticoagulation until platelet count recovery and perhaps longer if tolerated (four to six weeks after platelet count recovery) appears prudent by analogy with the duration of anticoagulation for classic HIT. It should be noted that the course of the initial patients is still unknown, and there are no data to guide decision-making, and this advice is likely to be amended as further data accrue (12,21).

Individuals who are discharged from the hospital and were taking a parenteral anticoagulant can be switched to a NOAC. Warfarin and other vitamin K antagonists (VKAs) should be avoided. At the same time, the patient is thrombocytopenic, due to the lack of efficacy during ongoing hemostatic activation. However, for an individual who is unable to receive a NOAC, a VKA might be an option following platelet count recovery, as long as appropriate bridging is used (10).

IVIG

High-dose intravenous immune globulin (IVIG), along with anticoagulation, is recommended to interrupt VITT antibody-induced platelet activation. A typical dose is 1 mg/kg intravenously once a day for two days (10,21).

It is important to continue monitoring the platelet count during hospitalization and following discharge from the hospital; because after IVIG administration, thrombocytopenia can recur within a few days after IVIG is completed (22).

Glucocorticoids

The limited information available on the management suggests that high-dose glucocorticoids can improve the platelet count within days in addition to intravenous immune globulin, which may limit the risk of hemorrhagic transformation, especially when anticoagulation is instituted (21,23).

Minimizing platelet transfusions

Platelet and/or the source of fibrinogen (fibrinogen concentrate, plasma, or cryoprecipitate) transfusions should be provided to patients with life-threatening complications, including bleeding or the need for emergency surgery, depending on the platelet count and fibrinogen level. Hematology and/or transfusion medicine input may be especially helpful in these cases (12).

Treatment of bleeding

Management of bleeding in VITT is especially challenging due to the competing goals of stopping bleeding and preventing thrombosis. General principles of managing concurrent bleeding and thrombosis should be followed with the opinion of a hemostasis specialist (12).

Monitoring

Clinical and platelet count monitoring for signs of thrombosis is critical. Platelet count monitoring is important in VITT because thrombocytopenia can recur after the effects of IVIG wear off. Other monitoring may include PT, aPTT, fibrinogen, and D-dimer, especially if abnormal (12).

We should continue inpatient management until the platelet count is >50,000/microL and improving for at least two to three days, the patient is on stable anticoagulation with no new or progressive thrombosis, there is no bleeding for at least two to three days, and appropriate follow-up has been assured(12).

Discharge

The duration of acute illness in VITT is unknown. The monitoring interval can be extended according to the patient's clinical status and platelet count (12).

CONCLUSION

Vaccination remains the most important solution to curb the COVID-19 pandemic. There is broad consensus that the benefits of vaccination greatly outweigh the potential risks of rare vaccine side effects, such as VITT.

Therefore, the importance of vaccination should be emphasized, and the primary criterion for the selection of vaccines is availability. For individuals who have access to more than one vaccine, the choice is individualized based on values and preferences. For individuals who have received one dose of the ChAdOx1 nCoV-19 vaccine, there

are no reliable data to support omitting the second dose or switching to a different vaccine; completion of the two-dose series is encouraged (12).

REFERENCES

1. Quazi S. Vaccine in response to COVID-19: Recent developments, challenges, and a way out. ***Biomed Biotechnol Res J*** 2021;5(2):105-9.
2. Chiluba BC, Dube G. Descriptive review of epidemiological geographic mapping of coronavirus disease 2019 (COVID-19) on the internet. ***Biomed Biotechnol Res J*** 2020;4:83-9.
3. Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, Evaluation, and Treatment of Coronavirus (COVID-19). 2023 Jan 9. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023.
4. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. ***JAMA*** 2020;324(8):782-93.
5. Langer F, Kluge S, Klamroth R, Oldenburg J. Coagulopathy in COVID-19 and Its Implication for Safe and Efficacious Thromboprophylaxis. ***Hamostaseologie*** 2020;40(3):264-9.
6. Nopp S, Moik F, Jilma B, Pabinger I, Ay C. Risk of venous thromboembolism in patients with COVID-19: A systematic review and meta-analysis. ***Res Pract Thromb Haemost*** 2020;4(7):1178-91.
7. White RH. The epidemiology of venous thromboembolism. ***Circulation*** 2003;107(23 Suppl 1):14-8.
8. Mazloomzadeh S, Khaleghparast S, Ghadrdoost B, Mousavizadeh M, Baay MR, Noohi F, et al. Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit: The INSPIRATION Randomized Clinical Trial. ***JAMA*** 2021;325(16):1620-30.
9. Cines DB, Bussel JB. SARS-CoV-2 Vaccine-Induced Immune Thrombotic Thrombocytopenia. ***N Engl J Med*** 2021;384(23):2254-6.
10. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. ***N Engl J Med*** 2021;384(22):2092-101.
11. Torjesen I. Covid-19: Risk of cerebral blood clots from disease is 10 times that from vaccination, study finds. ***BMJ*** 2021;373:n1005.
12. Warkentin TE, Cuker A. COVID-19: Vaccine-induced immune thrombotic thrombocytopenia (VITT). ***Update May*** 2021;7.
13. Scully M, Singh D, Lown R, Poles A, Solomon T, Levi M, et al. Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination. ***N Engl J Med*** 2021;384(23):2202-11.
14. Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, et al. Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. ***N Engl J Med*** 2021;384(22):2124-30.
15. Bourguignon A, Arnold DM, Warkentin TE, Smith JW, Pannu T, Shrum JM, et al. Adjunct Immune Globulin for Vaccine-Induced Immune Thrombotic Thrombocytopenia. ***N Engl J Med*** 2021;385(8):720-8.
16. https://theconversation.com/blood-clot-risks-comparing-the-astrazeneca-vaccine-and-the-contraceptive-pill-158652.
17. Gupta A, Sardar P, Cash ME, Milani RV, Lavie CJ. Covid-19 vaccine- induced thrombosis and thrombocytopenia-a commentary on an important and practical clinical dilemma. ***Prog Cardiovasc Dis*** 2021;67:105-7.
18. Oldenburg J, Klamroth R, Langer F, Albisetti M, von Auer C, Ay C, et al. Diagnosis and Management of Vaccine-Related Thrombosis following AstraZeneca COVID-19 Vaccination: Guidance Statement from the GTH. ***Hamostaseologie*** 2021;41(3):184-9.
19. https://thrombosiscanada.ca/covid-19-vaccines-and-blood-clots-faqs/.
20. https://www.isth.org/news/556057/ISTH-Statement-on-AstraZeneca-COVID-19-Vaccine-and-Thrombosis.htm.
21. Franchini M, Liumbruno GM, Pezzo M. COVID-19 vaccine-associated immune thrombosis and thrombocytopenia (VITT): Diagnostic and therapeutic recommendations for a new syndrome. ***Eur J Haematol*** 2021;107(2):173-80.
22. Thaler J, Ay C, Gleixner KV, Hauswirth AW, Cacioppo F, Grafeneder J, et al. Successful treatment of vaccine-induced prothrombotic immune thrombocytopenia (VIPIT). ***J Thromb Haemost*** 2021;19(7):1819-22.
23. Warkentin TE. High-dose intravenous immunoglobulin for the treatment and prevention of heparin-induced thrombocytopenia: a review. ***Expert Rev Hematol*** 2019;12(8):685-98.