Antithrombotic therapy in patients with COVID-19: indications, pharmacotherapy and controversy

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Hypercoagulability associated with COVID-19 infection increases risks for either venous or arterial thrombotic events (ATEs) or both.1 For hospitalised patients with COVID-19, the incidence of venous thromboembolism (VTE) was 4.5%,2 the rate among patients with critical illness was 27.9% as compared with those not critically ill (7.1%). The exact mechanism of COVID-19-related thrombotic events is unclear. However, it may partially be related to Virchow triad: alternation of blood flow (stasis), vascular endothelial injury by SARS-CoV-2 virus and alteration of the constituents of the blood including inherited or acquired hypercoagulable state. Therefore, it is a challenge to evaluate the thromboembolic risk, select an appropriate antithrombotic agent and decide on the doses and duration of therapy in these patients. Several international and American societies have published clinical guidelines that reviewed evaluation of coagulation abnormalities in patients with COVID-19.3–6 To balance the risk of bleeding and preventing or treating thromboembolic events, a simplified practical summarisation is needed.

MONITORING OF COAGULATION PARAMETERS IN PATIENTS WITH COVID-19 INFECTION

Such monitoring will be based on the severity of COVID-19 infection. For outpatients, no routine coagulation testing is indicated unless they developed symptoms of thromboembolism. For inpatients, must-do tests should include complete blood count with platelet, prothrombin time and activated partial thromboplastin time (aPTT), fibrinogen and d-dimer on admission. Other inflammation markers including C reactive protein, ferritin, interleukin-6 may also be considered. Daily trends of these test results may be needed for patients with higher acuity. The essays for factor VIII, VWF antigen and antithrombin III, protein C and S may also be considered if thromboembolism is detected regardless of the severity of COVID-19 infection.

The Wells’ criteria (table 1) have been widely used to evaluate the probability of VTE including deep vein thrombosis (DVT) and pulmonary embolism (PE).7,8 When the probability is low for PE or DVT, a low level of D-dimer (≤500 ng/mL) can rule out possible VTE events. A d-dimer level of ≥500 ng/mL may suggest the need for further imaging studies. Note: An ‘age × 10’ cut-off should be safe for patients ≥50 years. For example, the cut-off for a 65-year-old person will be 650 ng/mL.

Compressive ultrasonography is indicated for suspected DVT in symptomatic extremities, especially when the d-dimer is higher than the cut-off line. In patients with suspected PE, CT angiography (CTA) of pulmonary arteries are indicated. A ventilation/perfusion scan if CTA cannot be done due to impaired renal function (GFR <30), or CTA shows an
Prophylaxis dose of anticoagulation is appropriate for those hospitalised with an incidental positive COVID-19 test.

Postdischarge in an outpatient setting

One trial compared rivaroxaban 10 mg daily versus placebo for 35 days postdischarge and found a 67% relative risk reduction in their primary outcome without an increased risk of bleeding. However, a trial compared aspirin 81 mg daily versus apixaban 2.5 mg two times per day versus apixaban 5 mg two times per day versus placebo for 45 days and found no difference in the composite clinical outcome among four groups. Thus extended postdischarge routine use of antiplatelet or anticoagulation therapy is not recommended unless patients are discharged with a diagnosis of VTE or ATE.

Choice of anticoagulation agent and monitoring

Low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) are preferred unless there is a contraindication, such as severe thrombocytopenia (<50 × 10^3/L).

In hospitalised non-ICU COVID-19 patients without signs or symptoms of thrombosis, subcutaneous injection of LMWH such as enoxaparin 1 mg/kg two times per day to reach an anti-Xa level between 0.5 and 1 anti-factor Xa units/mL within 4–6 hours of starting LMWH. However, in morbidly obese patients with a body mass index ≥40 kg/m², or a weight ≥150 kg, or a severe renal insufficiency (creatinine clearance of ≤30 mL/min), IV UFH is preferred to reach an aPTT level of 2–3 times of the baseline. UFH molecules are distributed less to the adipose tissue than LMWH. Anticoagulation should continue for 3 months for provoked thromboembolism until clinical signs and symptoms of VTE or arterial embolism are resolved and no imaging findings of thrombus. Choices for outpatient anticoagulation include direct oral anticoagulants (DOACs) such as rivaroxaban, apixaban or dabigatran, and warfarin (international normalization ratio of 2–3). DOACs can also be considered if drug–drug interaction of LMWH or UFH with dexamethasone and antiviral agents for treating COVID-19 is of concern.
Choice of antiplatelet agents

The usefulness of aspirin in preventing thromboembolism in patients with COVID-19 is controversial. One trial studied aspirin 150 mg daily versus no aspirin and found that patients in the aspirin group had a slightly higher chance (75% vs 74%) to be discharged alive within 28 days, had less thrombotic events (4.6% vs 5.3%) but a higher chance of major bleeding events (1.6% vs 1.0%).

There are no data on the role of other antiplatelet agents for prophylaxis against thromboembolism in patients with COVID-19 infection.

COVID-19 INFECTION AND THROMBOEMBOLISM OF THE CENTRAL NERVOUS SYSTEM

COVID-19 infection may increase the risk of IS. The underlying causes include artery to artery emboli, cardioembolic emboli, microangiopathy due to disseminated intravascular coagulopathy and hypoxia. Early detection and timely treatment may help resolve or prevent a stroke.

When a patient’s mental and neurological status cannot be adequately assessed, such as in those on life support, a screening brain imaging should be performed. Intravenous thrombolysis is controversial for patients with COVID-19 who have an acute IS due to possible higher percentage of symptomatic intracranial haemorrhage. Otherwise, antiplatelet medications are indicated for secondary stroke prevention.

Cerebral venous sinus thrombosis (CVST) is a life-threatening condition that has been seen in patients with COVID-19 infection. When a COVID-19 patient has signs and symptoms related to the elevated intracranial pressure such as severe headache, visual disturbances and/or decrease level of consciousness, CT venography, MR venography or digital subtraction venography of the brain can help diagnosing a CVST. Although with no clear guidelines, therapeutic anticoagulation is indicated but with caution since brain parenchymal petechiae or haemorrhage or thrombocytopenia are often present with a COVID-19 infection. Close monitoring of coagulation profiles and routine use of CT of head or MRI may be indicated when anticoagulation therapy is in-progress. The duration of anticoagulation for CVST is inconclusive. Full anticoagulation may need to be continued until COVID-19 has been treated and there are no neuroimaging signs of CVST.

CONCLUSION

For outpatients with COVID-19 infection, no routine prophylactic anticoagulation is needed. Once they are hospitalised, therapeutic anticoagulation for non-ICU patients may shorten the days requiring organ support but with higher risk of bleeding. For ICU patients, prophylactic anticoagulation should be considered in those with no VTE, not on anticoagulant prior to admission and no arterial thromboembolism. Postdischarge, these patients do not require extended antithrombotic therapy unless they have a confirmed diagnosis of VTE or ATEs.

REFERENCES