Stroke and Thromboprophylaxis in the Era of COVID-19

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Introduction

In the rapidly evolving COVID-19 pandemic, many patients presenting with acute ischemic stroke may be potentially infected with the Severe Acute Respiratory Syndrome Coronavirus (SARS CoV-2) agent. As stroke patients are often unable to give an adequate history of preceding COVID-19 symptoms, all stroke patients in areas with high prevalence of community transmission should be considered potential cases. Observational studies have suggested an increased tendency for thrombotic events in patients infected with SARS CoV-2. These events include cryptogenic strokes with large vessel occlusion predominance,[1,2] deep-vein thrombosis (DVT) and pulmonary embolism (PE).[3–5] Acute ischemic stroke is associated with rates of DVT as high as 50%,[6] in the absence of COVID-19. Although acute stroke management algorithms in the COVID-19 pandemic have been proposed,[7–9] it is as important to review updated information on thromboprophylaxis during the COVID-19 pandemic for acute stroke patients and to develop practice guidance for the prevention of DVT and PE in this population.

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Current guidelines for thromboprophylaxis post-acute stroke

Acute ischemic stroke patients have a high risk of developing DVT and PE. Without prophylaxis, the risk of developing DVT is estimated at 50% within two weeks after the presenting stroke,[6] This risk is greatest in the first week after the stroke and can lead to potentially fatal PE. Patients with hemiparesis or atrial fibrillation are at increased risk of developing DVT.[6] Untreated symptomatic DVT can also result in post-thrombotic syndrome. International guidelines currently recommend pharmacologic prophylaxis for venous thromboembolism for acute stroke patients with restricted mobility[9] (see Table 1).

Mechanical thromboprophylaxis

A thigh-length intermittent pneumatic compression (IPC) device is recommended for most patients.[6] In the CLOTS 3 trial, the use of IPC compared to no IPC reduced the rate of DVT by 3.6% (95% CI 1.4−5.8)[10] , including both symptomatic and asymptomatic DVT. While the patients treated with IPC had a higher rate of skin breaks, no major adverse effects were seen.[10] Contraindications to IPC include patients with dermatitis, leg ulcers, severe edema, severe peripheral vascular disease and congestive heart failure[10]. They should not be used in patients with an established DVT. The risk of DVT is reduced even further with the combination of pharmacological prophylaxis and IPC.[11]

Pharmacological thromboprophylaxis

For patients with no contraindications, pharmacological prevention options include low molecular weight heparin (LMWH) or subcutaneous low-dose unfractionated heparin (UFH).[12–14] LMWH has a longer duration of action and more predictable pharmacodynamics when compared to UFH.[12] Additionally UFH carries higher risk of heparin-induced thrombocytopenia[15] compared to LMWH. In a meta-analysis by Shorr et al, the use of LMWH compared to UFH was associated with a significant risk reduction for

Table 1. *Standard post stroke DVT Prophylaxis*

Condition	Modification of Treatment
After intravenous thrombolysis	IPC on admission,* anticoagulation delayed until 24 hours after intravenous thrombolysis
No intravenous thrombolysis	IPC on admission,* low-dose LMWH/heparin
Already on anticoagulation	IPC on admission,* low-dose LMWH/heparin added only if full-dose anticoagulation is stopped
Contraindication to anticoagulation	IPC alone*

*IPC contraindicated in patients with dermatitis, established DVT, leg ulcer, severe edema, severe peripheral vascular disease and CHF

VTE, with an odds ratio (OR) of 0.54 (95% CI 0.41−0.70, $p < 0.001$) and PE (OR, 0.26; 95% CI 0.07−0.95; $p = 0.042$).[15] Despite these studies the overall benefit of pharmacological thromboprophylaxis in stroke patients is inconclusive as a mortality or functional status improvement is not seen on follow up.[9] While there is a lower risk of DVT with LMWH or UFH, this is offset by an increased risk of symptomatic bleeding.[9,16] In a meta-analysis by Whiteley et al. reduction in mortality was not documented with LMWH or UFH prophylaxis in stroke patients.[17] Guidelines recommend that where pharmacological prophylaxis is used, it should be delayed for 24 hours after the administration of thrombolytic therapy.[18]

Risk of thrombosis with COVID−19

COVID-19 has been associated with prominent features of widespread inflammation and a prothrombotic coagulopathy.[5,19] The rate of thrombotic complications in patients with severe COVID-19-related pneumonia admitted to an ICU was reported to be as high as 49%.[4,19] These events include both venous (96.3%) and arterial (3.7%) events. Other centers have reported rates of DVT of 25%[20] and PE of 20.6%.[3] These rates may be underreported due to incomplete follow-up in patients that were still hospitalized at the time of these publications. Poissy et al. reported that over 90% of patients who later developed PE were already on thromboprophylaxis.[3]

COVID-19 has been associated with several coagulation abnormalities. The most common are elevated rates of D-dimer, which is indicative of increased thrombin generation and has been correlated with mortality.[5, 21] Prothrombin time has been found to be modestly prolonged in COVID-19 patients and again associated with higher mortality.[22] Thrombocytopenia is inconsistently associated with COVID-19 severity.[22] Limited data are available on disseminated intravascular coagulation (DIC): in one report low fibrinogen levels as a marker of DIC were present in 71.4% of patients who later died, compared to 0.6% of survivors.[22] This is in contrast with other studies showing elevated fibrinogen levels and overt DIC being relatively rare.[23,24] Thromboelastometry studies have suggested a severe underlying inflammatory prothrombotic state that is driven by fibrinogen, and platelet activation to a lesser extent, rather than a consumptive coagulopathy.[24] Nevertheless, there has been considerable interest in the prognostic implications of an elevated fibrinogen and its use as a marker of illness severity.[25]

Recent data published by Tang et al. suggest that COVID-19 patients with a D-dimer level greater than 6 times normal or elevated sepsis-induced coagulopathy (SIC) scores > 4 may derive a mortality benefit from thromboprophylaxis at doses of 40−60 mg of enoxaparin or 10000−15000 units of heparin daily.[22] Additionally, patients who weigh greater than 100 kg may benefit from higher doses of thromboprophylaxis.[4]

Patients who are hospitalized with COVID-19 infection are also at increased risk of stroke and rates have been reported ranging from 0.9%[2] amongst all hospitalized patients in the US to 4.5% in intensive care unit patients in China.[26] In the critically ill, the PREVENT trial demonstrated no reduction in the incidence of proximal DVT from adjunctive use of IPC in patients already prescribed drug prophylaxis with UFH or LMWH.[27] This large trial however was not limited to high-risk stroke patients and was conducted prior to the SARS CoV-2 pandemic. Given the prothrombotic nature of coronavirus and limited evidence of harm, IPC should be considered in all critically ill COVID-19 patients. Pharmacological thromboprophylaxis should be prescribed for hospitalized COVID-19 patients, but currently there appears to be little evidence to support routine therapeutic anticoagulation for this population. The use of D-dimer guided anticoagulation in COVID-19 patients is currently being investigated in the PROTECT COVID trial.[2]

Stroke and COVID-19 thromboprophylaxis

Strokes, particularly those resulting from large vessel occlusion, are associated with certain prothrombotic states and the ensuing immobility and/or acute hospital care can compound the risk for thrombotic complications. There may also be an increased risk of stroke due to the inflammatory prothrombotic state in both symptomatic and indolent SARS-CoV-2 infection.[1] Therefore, particular attention should be given to thromboprophylaxis in this population. In patients who have undergone intravenous thrombolytic therapy, thromboprophylaxis should be

initiated as soon as the post-thrombolysis 24 h interval has elapsed, and repeat CT demonstrates no haemorrhage or indication for craniectomy.[9] In patients who have not undergone intravenous thrombolytic therapy, thromboprophylaxis can be initiated upon admission, in the absence of high-grade hemorrhagic transformation (i.e. parenchymal hematoma 1 or 2).[9] IPC should be used for all patients without contraindications, and pharmacological VTE prophylaxis should be strongly considered for all COVID-19 patients. Patients who are already anticoagulated should not receive additional doses of pharmacological VTE prophylaxis. The choice of drug will largely depend on local guidelines or institutional preference, however altered pharmacokinetics in the critically ill should be considered in addition to the potential prothrombotic state generated by COVID-19. Some centers have initiated regular assessment of coagulation factors with measurement of fibrinogen and d-dimer, and introduced higher intensity thromboprophylaxis regimes and therapeutic anticoagulation in selected patients (Table 2).[28]

Anticoagulation considerations in COVID-19 patients who develop stroke

A situation that warrants consideration is that of patients hospitalized because of COVID-19 infection who have had VTE prophylaxis initiated on admission, and subsequently developed a large vessel ischemic stroke, an occurrence with a reported frequency up to 4.5%.[23] Such an event may suggest that the routine VTE prophylaxis was unable to mitigate the prothrombotic state of COVID-19, raising the issue of whether escalation to full therapeutic anticoagulation is indicated in this instance. Although there are no current data to inform such decision, it may be reasonable to consider therapeutic anticoagulation in the event of the ischemic stroke(s) involving multiple vascular territories (thus suggesting an embolic phenomenon), provided there is no imaging evidence of large territory infarct or hemorrhagic transformation of the new infarct(s). Similar considerations would likely apply to the occurrence of a single large-vessel ischemic stroke while on VTE prophylaxis, with the caveat that the risk/benefit balance of escalation to therapeutic anticoagulation should take into consideration not only the presence of hemorrhagic transformation, but also the size of the infarct, a factor known to correlate with risk of hemorrhagic transformation whilst anticoagulated.[29]

As COVID-19 patients with stroke have been reported to have elevated antiphospholipid antibodies, it may be appropriate to screen for them prior to deciding on the optimal antithrombotic agent in an individual case.[30] It is unclear whether these antibodies represent definite antiphospholipid syndrome and repeat testing should be performed. In patients who have a stroke and pre-existing indication for direct oral anticoagulant therapy, such as atrial fibrillation, it may be reasonable to consider a vitamin K antagonist or therapeutic heparin in the presence of elevated antiphospholipid antibodies due to the reported inferiority of rivaroxaban compared with warfarin in a recent randomized trial.[31] The role and efficacy of DOAC therapy in the COVID-19 population has not been established. Furthermore in the presence of renal impairment a vitamin K antagonist may be preferred.

Given the evidence that high D-dimer rates are associated with mortality and thrombosis,[5] monitoring COVID-19 patients with D-dimer, platelet count, fibrinogen, and PT can be considered. Routine therapeutic anticoagulation for patients with acute stroke in COVID-19 infection is not

Table 2. *Suggested pharmacological thromboprophylaxis regimes in stroke patients with suspected or confirmed COVID − 19 infection*

	Indication	**LMWH, Cr CL ≤ 30mL/min**	**Heparin, CrCL ≤ 30mL/min**
Standard dose	No additional identifiable risk factors	Enoxaparin 40mg once daily	Heparin 5000 U twice daily
Consider high intensity dose	Weight > 100kg SIC > 4 D-dimer > 6 fold normal	Enoxaparin^ 40mg twice daily	No bolus and low aPTT goal
Consider full anticoagulation#	Confirmed DVT or PE Established indication for anticoagulation Dialysis filter thrombosis High clinical concern and unable to perform confirmatory testing	1mg/kg enoxaparin^ twice daily	Bolus and standard aPTT goal 55-90 seconds

Progress CT should dictate timing of thromboprophylaxis in patients with large established infarcts. ^Consider anti-Xa monitoring in patients with extremes of body size and renal dysfunction.

indicated at this time due to the concerns for hemorrhagic transformation.[32] Surveillance for thrombotic events such as DVT and PE is encouraged for patients at high risk of VTE.

Critically ill patients with COVID-19, who require mechanical ventilation are at particularly high-risk for developing DVT/PE.[4,20] As thromboprophylaxis has been shown to be associated with reduced mortality in patients with elevated D-dimer,[22] several anticoagulation algorithms have been proposed in critically ill COVID-19 patients and adjusted for eGFR. In patients with altered mental status or focal neurological signs, it is appropriate to obtain a head CT prior to initiating anticoagulation to ensure there is no large infarction or hemorrhage.[32] There are reports of an increase in cerebral microhemorrhages in COVID – 19 patients but the clinical significance of this is unclear.[33] Close monitoring of PTT or anti-factor Xa levels may be necessary to ensure patients are not supratherapeutic. Neurological surveillance is also important in this population due to the risk of intracranial hemorrhage whilst on anticoagulation, with high associated mortality rates.[32]

Conclusions

DVT prophylaxis is standard of care for acute stroke patients. In the context of suspected or confirmed SARS-CoV-2 infection, there is an increased risk of VTE. As such, routine mechanical DVT prophylaxis and pharmacological thromboprophylaxis is recommended. Special consideration should be given to drug pharmacokinetics and pharmacodynamics, with increased dosing in patients with COVID-19, in the critically ill, or those with increased body habitus or documented coagulopathy. Currently there is insufficient evidence to routinely commence therapeutic doses of anticoagulation in this stroke population. Future studies may provide further guidance on targeted anticoagulation regimens in this patient group.

Declaration of Competing Interest

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