Review Article

COVID-19 and thrombotic complications—the role of anticoagulants, antiplatelets and thrombolytics

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Abstract

Coronavirus disease 2019 (COVID-19) is a global pandemic the world is dealing with currently. Clinical evidences suggest that the patients are predisposed to both venous and arterial thrombotic complications. This is because of severe inflammatory responses, injury to endothelium and activation of platelets leading to increased coagulation. Additionally, individuals who are already receiving antithrombotic drug therapy for various cardiovascular diseases and complications might contract the disease in which case, attention should be given to the choice and duration of the therapy besides close monitoring of biochemical blood parameters. Herein, we review the incidences of thrombotic complications and their outcomes in COVID-19 patients as reported till date, while understanding the prophylactic and therapeutic roles of anticoagulants, antiplatelets and thrombolytics in the management of this severe viral respiratory illness.

Keywords: Anticoagulant, antiplatelet, coronavirus disease 2019, SARS-CoV-2, thrombolytics, thrombosis

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has got numerous vital cardiovascular implications. Individuals with existing cardiovascular complications are at greater risk of contracting this viral disease. Additionally, there are an increasing number of evidences suggestive of high chances of thrombotic complications in patients with COVID-19.

Both direct effects of SARS-CoV-2 or secondary causes such as severe hypoxia and inflammation predispose patients to thrombotic complications. Preliminary reports are suggestive of disseminated intravascular coagulation occurring in such patients with increased levels of d-dimer and fibrin degradation products in addition to prothrombin time (PT) prolongation.[1] Additionally, the novel medicines being clinically investigated could have adverse drug–drug interactions with antiplatelets, thrombolytics and anticoagulants.

However, it is still not clear if these haemostatic changes are specifically related to COVID-19 or are due to the cytokine storm leading on to systemic inflammatory response syndrome, as commonly seen in viral diseases in general.[2]

Individuals with severe viral pneumonia and acute respiratory distress syndrome (ARDS) who require hospitalization are at 23 times higher risk of developing pulmonary embolism (PE)[3] and international guidelines recommend routine thromboprophylaxis.[4]

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Further, a trial subgroup analysis showed that extended regimen of thromboprophylaxis with direct orally administered anticoagulants (DOACs) in patients with raised d-dimer levels or who had been hospitalized due to infection especially pneumonia is more beneficial than in-hospital low molecular weight heparin (LMWH)-based thromboprophylaxis.[5] Additionally, empirical treatment with anticoagulants has led to improved thrombotic outcomes in individuals with ARDS due to H1N1.[3]

Continuously growing understanding of pathophysiology of the novel coronavirus has hypothesized the interplay of the direct effect on vascular endothelium and predisposing factors like hypoxia, severe inflammation and immobilization towards the thrombotic nature of the disease.[3] Post-mortem analysis and observational studies from various centres of the world have highlighted the higher incidence of thrombotic and thromboembolic diseases in COVID-19 patients, highlighting the importance of drugs targeting thrombosis in management of COVID-19.

Recent evidences suggest that COVID-19 can affect endothelial cells through activation of inflammatory[6] and complement pathways,[7] resulting in endothelial dysregulation, activation of leucocytes, complement deposition and activation of platelets. Additionally, hypoxia has also been suggested as a stimulus for thrombosis in patients of COVID-19 which might also explain the resistance seen in such patients to standard doses of heparin used for thromboprophylaxis.[8]

Primary objective of this article is to review the current evidences, recommendations and future prospects on the use of anticoagulants, fibrinolytics and antiplatelets in COVID-19 patients.

Clinical Evidences of Thrombotic Complications

The incidence of venous thromboembolism (VTE) in COVID-19 patients has been reported to be around 10–35% with autopsy data pointing towards a value as high as 60%.[9]

Among 81 severe novel coronavirus pneumonia patients enrolled in a study conducted by Cui *et al.* in Wuhan, China, 20 were found to develop lower extremity venous thrombosis amounting to 25% incidence of VTE.[10] Higher levels of d-dimer and PT have been shown to be associated with poor prognosis in patients with COVID-19.[1,10]

In a retrospective, multicentre cohort-based study done in Wuhan, China, which included 191 patients, increased concentration of d-dimer on admission (>1 μg/mL) was associated with 18 times higher chance of mortality than those with lower concentrations.[11]

In a study involving 184 COVID-19 patients admitted in the intensive care unit (ICU), cumulative incidence of both arterial (3.7%) and venous thrombotic events (27%) was found to be 31%. The incidence of thrombotic complications in COVID-19 patients admitted in the ICU was also notably higher when compared to non-COVID ICU patients.[12]

In a prospective, multicentre-based study, high risk of thrombosis was found in COVID-19 patients. Out of 150 patients, 64 different thrombotic complications could be identified.[13] PE was the major complication noted in 16.7% of the patients. Von Willebrand Factor activity, besides the levels of factor VIII, was considerably raised in the affected patients; 87.7% were positive for lupus anticoagulant. Majority had raised levels of d-dimer and fibrinogen.

A large study reported from China, which included 1099 COVID-19 patients from 552 hospitals, pointed out that d-dimer concentrations were >0.5 mg/L in 46.4% of the patients, out of which 60% had developed severe ARDS. In these subsets of patients, the d-dimer levels were almost 4 times higher (mean level of 2.12 mcg/mL) compared to non-severe patients (mean level of 0.61 mcg/mL).[14]

A study on 101 COVID-19 patients undergoing duplex ultrasound for clinically suspected deep vein thrombosis (DVT) showed that 42 were having DVT while 24 had PE, out of which 8 were associated with DVT. The diagnosis was most commonly made in the first two weeks of hospital admission (73.8%).[15]

Irrespective of the COVID status, many predisposing factors for VTE such as prolonged bed rest and severe infection are shared among most ICU admitted patients. However, as mentioned earlier, it seems additional pathological mechanisms like endothelial damage, microvascular thrombosis, occlusion and autoimmune pathways might contribute to the excessive coagulation activation in patients with COVID-19.[16,17]

The peculiar histopathological findings of the lung tissue in 38 COVID cases from Northern Italy revealed atypical pneumocytes (reactive atypia) and diffuse thrombosis of the peripheral small vessels. Fibrin thrombi were observed in the small arterial vessels (diameter <1 mm) of 33 patients, with >25% of tissue involvement along with elevated d-dimer blood levels in half of them.[18] Along with the pulmonary interstitial fibrosis and infarct, similar microscopic findings of vascular wall thickening, lumen stenosis and occlusion were also noted in dissected lung specimens of patients in Shenzhen, China.[19] These findings reinforce the underlying abnormal coagulation mechanism in COVID-19 patients and the further need to explore likely benefits of anticoagulation (AC) therapy in such cases.

We hereby discuss the evidences for different classes of drugs, mainly used for thromboembolic disorders, in the management of thrombotic complications in COVID-19.

Anticoagulants

Heparin use is preferred over other anticoagulants owing to its pluripotent nature of being able to act as an anticoagulant, anti-inflammatory (decreases pulmonary inflammation and improves oxygenation) and antiviral agent. Theoretically, heparin could block the formation of thrombin and hence attenuate inflammatory responses. Further, it might also possess antiviral potencies by acting on host cell angiotensin-converting enzyme 2 and prevent the entry of SARS-CoV-2.[20] However, the chances of development of heparin resistance should be kept in mind, especially for those with the following: (a) antithrombin (AT) activity ≤60%, (b) platelet count of >300,000, (c) age ≥65 years and (d) elevated factor VIII and fibrinogen levels. Therefore, close monitoring of these parameters is a necessity in patients of COVID-19 receiving heparin. In cases where it is suspected, AT-heparin cofactor assay must be performed which takes into account the low activated partial thromboplastin time levels since it can act as a confounding factor.[13] For a COVID-19 patient admitted in the ICU, unfractionated heparin (UFH) is usually preferred over LMWH due to shorter duration of action and lesser interactions with any of the investigational drugs being tried against SARS-CoV-2.[21]

LMWHs have shown to have some degree of anti-inflammatory properties[22] which might be useful against the cytokine storm occurring in COVID-19 patients. Additionally, they have been associated with reduction of release and activity of IL-6[23] and inhibition replication of SARS-CoV.[24]

In a prospective multicentric study, despite the use of LMWH, a major fraction of the COVID-19 patients having ARDS developed fatal thrombotic complications.[13] Hence, the study concluded that higher doses of anticoagulants might be necessary in critically ill patients. Close monitoring of the therapy should be done through repeated anti-Xa measurement.

Findings from a large cohort involving 2,773 patients of COVID-19, who had been hospitalized and treated with treatment-dose AC, revealed no difference in overall mortality and survival outcomes among those who received AC as compared to those who did not receive AC. However, a significant difference was observed among mechanically ventilated patients ($N = 395$) who received AC as compared to the non-recipients of AC in terms of both in-hospital mortality (29.1% vs. 62.7%) as well as survival benefit (median survival: 21 days vs. 9 days). It's worthwhile to note that this New York-based study also reported that those receiving AC were more likely to require invasive mechanical ventilation (29.8% vs. 8.1%, $P < 0.001$). Further, longer treatment duration was found to be associated with mortality benefits (adjusted hazard ratio of 0.86 per day, $P < 0.001$).[25]

In a retrospective study on 449 severe COVID patients, a 28-day mortality was compared between heparin users and nonusers. The heparin treatment, given at prophylactic doses mainly with LMWH, demonstrated no mortality difference in heparin user versus nonuser. However, on stratified analysis, heparin use was found to be associated with mortality benefits in those with sepsis-induced coagulopathy (SIC) score ≥4 (40.0% vs. 64.2%, $P = 0.029$), but no mortality benefits were seen in those with SIC score <4, suggesting a selective anticoagulant benefit to only patients with higher SIC scores.[26]

A meta-analysis considering 11 observational studies showed that 23.9% of the hospitalized COVID-19 patients developed VTE in spite of receiving anticoagulants.[27] Another 12-studies-based meta-analysis indicated a 31% pooled prevalence of VTE among patients admitted in the ICU and receiving LMWH or UFH as thromboprophylaxis.[28] Considering the occurrence of VTE despite anticoagulant-based therapy, intensified regimens have been suggested. However, bleeding complications associated with such regimens might be a hindrance in their adoption.

The interim guidance formulated and released by the WHO recommends once daily LMWHs or UFH twice daily prophylactically. Missed doses of the prophylaxis are likely to be associated with fatal outcomes, and hence, every effort should be made to ensure the compliance of the schedule. In this regard, once-daily LMWH dosing would be more advantageous over UFH.[29]

In terms of post-discharge advice for a patient with any acute illness, prophylaxis using LMWHs and oral anticoagulants reduces the chances of VTE at the cost of increased chances of bleeding. With no COVID-19-specific evidence, the risk stratification needs to be done on a case-to-case basis following recommendation of an extended prophylaxis (up to 45 days) for individuals with high risks of VTE such as those having comorbidities like diabetes and cancer and with raised d-dimer levels (more than twice the normal upper limit) having less bleeding risks.[30]

Recently, the Massachusetts General Hospital has released a treatment guideline for haematological issues management in COVID-19. All individuals with COVID-19 would be receiving standard prophylactic dose of LMWHs unless there is any contraindication. In case of renal impairment (CrCl < 30 mL/min), UFH would be preferred over enoxaparin sodium 40 mg subcutaneous injection once daily. Patients who are already on some DOAC or warfarin on an outpatient basis (atrial fibrillation, past VTE or prosthetic heart valve) and those with diagnosed acute DVT or PE would be given therapeutic doses of LMWH. Administration of any advanced therapy such as tissue plasminogen activator (TPA) is not mentioned in the guideline, neither does it mention the usage of antiplatelets.[31]

The International Society of Thrombosis and Haemostasis (ISTH) interim guidance on recognition and management of coagulopathy in COVID-19[32] recommends the use of LMWHs in all patients (irrespective of their severity) who require hospitalization unless there are contraindications – active bleeding and platelet count $<25\times10^9$/L). Strict monitoring has

been prescribed in case of severe renal impairment. In case of bleeding episodes, a strategy similar to septic coagulopathy (as per the ISTH guidelines) considering blood transfusions is to be followed.[33]

Recent evidences also point towards a need for post-discharge thromboprophylaxis. A retrospective study on 163 COVID-19 patients, who were discharged from hospital without any advice for anticoagulants, showed 2.5% (95% CI: 0.8–7.6) incidence of thrombosis with a clinically relevant but nonmajor bleeding incidence of 2.9% (95% CI: 1.0–9.1).[34]

Tissue Plasminogen Activator

Animal models[35,36] and an early phase clinical trial[37] results have supported the use of plasminogen activators to reduce ARDS-related deaths. Although the clinical trial involved the use of urokinase and streptokinase, the more recent approaches recommend TPA use owing to its higher efficacy lysis of clot. Further, in a meta-analysis of preclinical data, it was reported to be associated with greater reduction in mortality, higher increase in arterial partial pressure of oxygen and larger fall in the level of arterial partial pressure of CO_2 as compared with controls not receiving any treatment, than urokinase-plasminogen activator combined, although none of the studies was based on virus-induced ARDS.[37] A special report on the role of TPA for COVID-19 management suggests a loading dose of 25 mg over 2 h and a maintenance dose of 25 mg infusion over the next 22 h with a maximum dose of 0.9 mg/kg. Considering the same exclusion criteria used for myocardial infarction and stroke, the patients who respond should be put on short-term heparin following TPA treatment. COVID-19 patients having ARDS with pO_2/FiO_2 (P/F) value <60 and a pCO_2 >60 even after prone positioning and maximum support in a mechanical ventilator should be considered for this treatment, especially when extracorporeal membrane oxygenation is not available. In addition, if there is lack of availability of ventilators, TPA could be given to those with rapidly progressive pulmonary deterioration.[38]

A few case reports on the use of alteplase in critically ill patients of COVID-19 with severe ARDS who have been mechanically ventilated demonstrated an initial improvement in their P/F ratio. Although the initial improvements were short-lived and the conditions gradually worsened in all the patients after receiving the complete dose of their TPA infusion, a proposal on considering different TPA regimen with varying doses, with or without AC therapy, has been made.[39] Further, a case series of four COVID-19 patients in respiratory failure with shock advocates for the use of low-dose TPA with concomitant heparin, demonstrating fast and considerable improvements in alveolar ventilation, arterial oxygenation and/or shock.[40] In both of these studies, TPA was given in dose of 50 mg over 75 min to 2 h, followed by slow prolonged infusion.

There is a practice of administering much higher bolus doses of TPA along with an UFH drip in cases such as sub-massive PE; 100 mg bolus dose of alteplase, along with a therapeutic UFH drip, has been associated with reducing mortality with a minor increase bleeding risk by 1.2%.[41] Wang *et al.* have suggested the use of larger TPA bolus doses (50 mg/100 mg) without stoppage of anticoagulants to prevent recurrent episodes of pulmonary thrombosis in patients of COVID-19 with ARDS.[39] Further, the minimal chance of fatal bleeding due to TPA in non-stroke patients should also be weighed against the benefits of the agent.[1]

A study based on predictive analytics using Markov state transition model suggested that the use of TPA might improve the prognosis of COVID-19 patients with ARDS.[42] Several centres in the USA have formulated protocols for salvage use of systemic TPA for this disease.[38]

A retrospective study reported the impact of thrombolysis using alteplase in 12 COVID-19 patients who were on either mechanical ventilator or continuous positive air pressure. Five of them had multi-organ dysfunction syndrome and required haemodialysis. The P/F ratio post-thrombolysis showed significant improvements in all of them. Seven patients finally got discharged while the remaining five died due to multi-organ failure.[43]

Antiplatelets

Considering that autopsy findings in COVID-19 suggest platelet-rich thrombi, there is curiosity whether antiplatelets can have beneficial effects in reducing thrombosis. Clinical data evaluating role of antiplatelets as thromboprophylaxis are scarce as compared to anticoagulants.

Aspirin has got pleiotropic effects of interfering with the virus replication process, AC and acting as an anti-inflammatory agent; but it has not been studied and considered on a major scale against SARS-CoV-2. One in-vivo animal study showed the inhibitory effect of aspirin on viral replication done via inhibiting prostaglandin E2 in macrophages and upregulating type I interferon production.[44] It should be considered for patients with elevated troponin levels along with cardiac dysfunctions, especially with increased maximum amplitude in thromboelastography.[45]

Recently, a randomized controlled trial (RCT) named Protective Effect of Aspirin on COVID-19 patients has started enrolling patients. Low dose aspirin (100 mg/day) would be given to the patients in the treatment arm in addition to the routine care. The primary outcome measures of this trial are time to clinical recovery and time of SARS-CoV-2 overcasting in the upper respiratory tract specimens.[46]

Dipyridamole is a phosphodiesterase (PDE) inhibitor which is used as an antiplatelet drug. Besides its already established antiplatelet function, it might provide therapeutic benefits to patients of COVID-19. Several studies including clinical trials[47-50]

have pointed towards its broad-spectrum antiviral properties, especially against positive-stranded RNA viruses.[47] Further, it also acts as an anti-inflammatory agent while promoting mucosal healing.[50] Additionally, being a pan-PDE inhibitor, it might lead to acute damage and progressive fibrosis of various organs such as the lung, heart, liver and kidney.[51]

A study exploring the therapeutic benefits of dipyridamole in critically ill COVID-19 patients showed that dipyridamole can suppress SARS-CoV-2 replication in Vero E6 cells. Fifty milligram oral tablets were administered three times daily for 14 consecutive days. The EC_{50} value for the suppression of the viral replication was 100 nmol/L, indicating that the therapeutic dose of the drug may lead to effective antiviral responses in COVID-19 patients. Additionally, adjunct administration of the drug along with routine care correlated well with improved prognosis and remission rates. Dipyridamole use also led to better coagulation profile by limiting the rise in d-dimer concentration and improving the platelet and leucocyte count, besides promoting recovery of the immunological cells. All the eight critically ill patients, who received dipyridamole, showed markedly improved clinical responses; 87.5% discharged from the hospitals and the rest showed clinical remission. On the other hand, out of the 12 critically ill patients in the control group, only one-third was discharged with death occurring in 16.7%.[49]

A prospective multicentre randomized controlled trial named C-19-ACS has started enrolling COVID-19 patients who require hospitalization. Cardioprotective drugs like aspirin, clopidogrel, rivaroxaban, atorvastatin as well as omeprazole have been considered as interventional agents for the various treatment arms.[52]

Conclusion

Thrombotic diseases might be both risk factors as well as complications associated with COVID-19. Recent evidences point towards a probable prophylactic and therapeutic roles of anticoagulants, antiplatelets and thrombolytics in the management of the disease. A couple of ongoing RCTs aim to estimate the effective treatment regimen for both ICU and non-ICU patients – CORIMMUNO-COAG (NCT04344756) comparing tinzaparin or UFH with local standard of care[53] and COVID-HEP (NCT04345848) comparing therapeutic versus prophylactic AC.[54] More of such RCTs are needed to establish the role of antiplatelets, anticoagulants and fibrinolytics in the clinical management of COVID-19 and expand our armoury against this global pandemic.

The key messages, as also have been summarized in Table 1, are: Evidences suggest that COVID-19 predisposes patients to thrombotic complications, the use of heparin has been recommended by international guidelines and that there are potential therapeutic roles of antiplatelets and thrombolytics besides anticoagulants which have been delineated in this review. Since COVID-19 is here to stay for a while and prevalence of this public health problem is on the rise, it is highly important for family physicians and primary care specialists to have knowledge of the possible thrombotic complications and their prevention cum management guidelines. As India continues to fight this pandemic with a highly skewed doctor-to-patient ratio, it is necessary that all healthcare professionals join hands together and treat patients in an evidence-based manner. As more and more information on thrombosis and its consequences in COVID-19 come to the forefront each day, this review will serve as a guiding document on the current consensus of anticoagulant-based management of thrombotic complications in COVID-19 in addition to the roles of antiplatelets and fibrinolytics.

Table 1: Summary highlighting some of the key points in diagnosing and managing thrombotic complications in COVID-19 patients

Key points
Coronavirus Disease 2019 (COVID-19) patients are at higher risk of developing arterial and venous thrombosis that leads to mortality and is caused by inflammatory and complement pathways activation, endothelial dysregulation, complement deposition and platelet activation
Biomarkers of coagulation and inflammation have been proposed to be important tools to diagnose and understand the prognosis of the thrombotic complications - d-dimer is the most commonly used marker in clinical practice
Current guidelines and evidence-based approaches guide us to provide thromboprophylaxis and manage thrombotic complications in COVID-19 patients
At times of public health crisis such as the ongoing pandemic, family physicians and primary care specialists need to play a major role in diagnosing such thrombotic complications and provide guideline-directed treatment besides prescribing thromboprophylaxis to high-risk COVID-19 patients

Ethical approval and patient consent

Not required.

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Conflicts of interest

There are no conflicts of interest.

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