EDITORIAL

COVID-19 Associated Arterial and Venous Thromboembolism

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COVID-19 or 2019 novel Coronavirus disease is a clinical syndrome caused by infection with the SARS CoV-2 (severe acute respiratory syndrome novel Coronavirus 2) and it has imposed an overwhelming burden on healthcare infrastructure all over the world. COVID-19 is a multisystem disease characterized by systemic inflammation, cytokine storm, elevations in biomarkers of cardiac injury, endothelial dysfunction and microthrombi formation. SARS-CoV-2 is a single-stranded RNA coronavirus, which enters human cells by mainly binding the angiotensin-converting enzyme receptor, which is highly expressed in lung alveolar cells, cardiac myocytes, the vascular endothelium, and other cells (1).

COVID-19 infection leads to a prothrombotic state which could be a consequence of increased coagulation, decreased fibrinolysis or immune effects. COVID-19 is associated with abnormalities in all the components of Virchow's triad causing an increased risk of venous thromboembolism (VTE). Endothelial dysfunction may develop as a result of direct viral invasion of endothelial cells via Angiotensin Converting Enzyme-2 receptors, or due to the subsequent marked inflammatory response and tissue hypoxia (2,3). Endothelial damage and disruption of intercellular junctions in COVID-19 exposes the subendothelial matrix containing tissue factor and collagen (4). This activates the coagulation cascade and results in thrombin generation; conversion of fibrinogen to fibrin which in combination with platelet aggregation leads to thrombus formation. COVID-19 induces a pro-coagulant state with an increase in factors V, VII, VIII and X and von Willebrand factor (2). Furthermore, reduced fibrinolysis resulting from increased plasminogen activator inhibitor 1 has been observed in both ICU setting as well as non-ICU patients (2). Immobility and resultant venous stasis are common, especially in more severe forms of COVID-19 infection predisposing to venous thromboembolism.

Pulmonary embolism in Covid-19 infection may be secondary to deep venous thrombosis or there may be in-situ immunothrombosis in smaller pulmonary arteries and capillaries related to a distinct COVID-19 pulmonary intravascular coagulopathy (2).

One of the most consistent findings associated with thromboembolic phenomenon in Covid-19 infection is raised D-dimer, fibrin or fibrinogen degradation products. High D-dimer levels may be representative of fibrin breakdown or increased fibrin turnover due to severe lung inflammation. Elevated D-dimer levels at admission are associated with increased risk of in-hospital mortality (5). Other coagulation abnormalities observed in patients with severe COVID-19 include mild thrombocytopenia or a mild increase in the prothrombin time (2).

According to a recent metanalysis, the incidence of venous thromboembolism (VTE) in patients of Covid-19 infection was found to be 26%. Pulmonary embolism (PE) occurred in 12% of patients and deep vein thrombosis (DVT) alone in 14%. VTE occurred in 24% patients in intensive care units (ICU) and 9% patients in wards, PE

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occurred in 19% and 4% patients in ICU and wards respectively whereas DVT alone was seen in 7% patients in both wards and ICU's (6). Overall rate of arterial thromboembolism in covid-19 patients was 2% whereas it was 5% in ICU patients. The mortality rate among patients with thromboembolism was 23% compared to 13% among patients without any thromboembolic episodes (7).

There should be a low threshold for diagnosing thromboembolic complications in Covid-19 patients. Symptoms like leg pain and swelling typical of deep vein thrombosis (DVT) or signs and symptoms suggestive of pulmonary embolism like sudden worsening of hypoxaemia, significant drop in blood pressure, new onset tachycardia or disproportionate requirement of oxygen to the severity of pneumonia on imaging or acute unexplained right ventricular dysfunction should be actively investigated. Definitive imaging like CT pulmonary angiography for PE and compression venous Doppler of lower limbs for DVT should be undertaken wherever feasible.

Therapeutic anticoagulation is the mainstay of VTE treatment. The vast majority of sick patients receive thromboprophylaxis after VTE risk assessment. Low-molecular weight heparin is the most commonly used form of anticoagulant used. D-dimer levels have been used in some institutions to guide anticoagulation, even in the absence of imaging detected VTE (2).

Post discharge, extended thromboprophylaxis may be considered if the patient is considered at high risk of VTE and the risk of VTE is felt to outweigh the risk of bleeding in the individual. Although there is no consensus regarding the optimal dose and duration of anticoagulation in such cases, but a standard prophylactic dose of Low molecular weight heparin or Novel oral anticoagulant (NOAC) for four weeks may be a reasonable approach.

Severe Covid-19 disease may be associated with myocardial injury indicated by elevated cardiac troponin levels or electrocardiographic and echocardiographic abnormalities (8). Some of these episodes of acute coronary syndrome may be due to plaque rupture (type 1 Myocardial Infarction). Efforts should be made to distinguish nonspecific myocardial injury and myocarditis from true plaque rupture myocardial infarctions prior to any intervention. Optimal medical therapy should be continued. However, non-urgent cardiac procedures may be deferred in order to preserve hospital resources and minimize exposure for health care workers as well as patients.

Till the time new evidence-based data emerges regarding the optimal management of arterial and venous thromboembolism in Covid-19 infections, it may be is prudent to use thromboprophylaxis in at least selected patients specially those who belong to the sickest sub-set after individualized assessment of the bleeding as well as thromboembolic risk in order to reduce the high morbidity as well as mortality associated with it.

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