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Case Report

Intracranial Hemorrhage Associated with Therapeutic Anticoagulation in Three Critically Ill COVID-19 Patients: A Case Series

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Abstract

Introduction: The COVID-19 pandemic has challenged global health with novel pathogenesis that is both severe and poorly understood. Several mechanisms have been proposed to explain the severity and complexity of the clinical illness including cytokine storm release, thromboembolic microangiopathy, direct cytotoxicity, and post-viral bacterial super infection.

Cases: The patients in this case series were all admitted to the intensive care unit with respiratory failure from COVID-19 requiring invasive mechanical ventilation. They were all started on anticoagulation. All three patients developed acute kidney injuries. The first patient had hypertensive emergency at the time of the bleed. The second and third patient both had supratherapeutic heparin levels at the time of the bleed.

Methods: We followed patients aged 18 years and above who were admitted to the ICU for COVID-19 during April and May 2020. We then followed those who required therapeutic anticoagulation for any indication and evaluated the ones that developed ICH.

Results: Out of the 79 patients admitted to the ICU for COVID-19 related illness during April and May 2020, 31 were placed on therapeutic anticoagulation (intermediate or full-dose) for indications that included hypercoagulable state, ACS, atrial fibrillation, and deep vein thrombosis. 25% of patients on anticoagulation developed bleeding for which the anticoagulation had to be stopped. Three out of these 31 patients developed ICH while on anticoagulation, accounting for 3.8% of our ICU population with COVID-19.

Discussion: Activation of coagulation pathways during cytokine storms can result in systemic thromboembolism, in both venous and arterial circulations posing risk of ischemic infarctions to any organ. Supratherapeutic heparin levels and acute kidney injuries are common in COVID-19 patients. The ideal candidates for anticoagulation, the recommended agent and dose, and duration of treatment remain unclear.

Conclusion: The benefits of anticoagulation should be weighed against the potential risk of bleeding.

Keywords: Acute kidney injury; Anticoagulation; Complication; COVID-19; Intracranial hemorrhage; Renal insufficiency; Therapeutic

Introduction

The COVID-19 pandemic has challenged global health with novel pathogenesis that is severe and lethal as well as poorly understood. Several mechanisms have been proposed to explain the severity and complexity of the clinical illness including cytokine storm release, thromboembolic microangiopathy, direct cytotoxicity, and post-viral bacterial super infection [1-3]. These proposed mechanisms led physicians to monitor laboratory parameters like C - reactive protein, d-dimer, and procalcitonin among others [1-3].

Several institutions have instated recommendations for venous thromboembolic (VTE) prophylaxis in COVID-19 infected patients, including evaluating d-dimer levels, however, the ideal candidates for prophylactic anticoagulation are yet to be identified, let alone selecting the effective agent and the appropriate dose [4].

With the increasing use of therapeutic dose anticoagulation, there has been a concern for an increased incidence of bleeds. We report a case series of 3 patients with COVID-19-related multi-organ failure whose course was complicated by intracranial hemorrhage.

Methods

We looked at the charts of patients aged 18 and above who were admitted to the ICU for COVID-19 during April and May 2020. We identified patients that required therapeutic anticoagulation and followed them to the time of disposition (death or discharge) to find the patients who developed ICH.

Case series

Case # 1: A 45-year-old female with no known co morbidities was admitted to the hospital with respiratory failure due to COVID-19 Pneumonia. Inflammatory markers and procalcitonin were elevated. Plasma exchange for the management of the cytokine storm and antibiotics for post-viral bacterial pneumonia were instituted. Due to concerns of COVID-19 related hypercoagulability, she received enoxaparin at 0.5mg/kg Q12H. On day 8 she was intubated and

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mechanically ventilated. Subsequently, anuric acute kidney injury required initiating hemodialysis and enoxaparin was switched to 8-hourly heparin of 7500 units subcutaneously due to renal failure. She developed hypertensive urgency requiring nicardipine drip which was eventually switched to oral amlodipine. After 15 days she improved and both mechanical ventilation and hemodialysis were stopped. Two days later, she became unresponsive and developed tonic-clonic seizure activity. The blood pressure at the time was 186/99. She was re-intubated for airway protection. CT head showed 2 foci of intracranial hemorrhage in the left posterior parietal and occipital lobes with no venous sinus thrombosis. Heparin was reversed with protamine sulfate. MRI of the brain confirmed the hemorrhage as well as surrounding vasogenic edema and diffuses FLAIR and density of the subcortical white matter, depicting posterior reversible encephalopathy syndrome.

Case # 2: A 62-year-old female with hypertension was admitted to the hospital with upper respiratory tract symptoms due to COVID-19 infection and was discharged after 48 hours. She was readmitted a week later with acute hypoxic respiratory failure and was started on remdesivir and broad-spectrum antibiotics for suspected superimposed pneumonia. On day 3, she developed respiratory failure requiring high-flow nasal cannula with severe due to diabetes insipidus. Due to concern for COVID-19 related hypercoagulability she was started on enoxaparin 40 mg subcutaneous twice a day. On day 4, she required mechanical ventilation and vasopressors. Due to acute kidney injury, continuous renal replacement therapy (CRRT) was initiated on day 6. On day 11, she developed bradycardia and significant troponin elevation for which heparin drip was started for non-ST-segment elevated myocardial infarction (NSTEMI). On day 12, PTT was greater than 139 seconds. On the same day she became unresponsive and a head CT showed a small hematoma within the left cerebellum. Heparin drip and antiplatelet therapy were discontinued. Repeat CT on day 20 revealed complete resolution of left cerebellar hematoma.

Case # 3: A 67-year-old female presented with altered mental status and acute hypoxemic respiratory failure secondary to COVID-19 pneumonia requiring mechanical ventilation. CT of the head showed no acute pathology. Antibiotics were started for Beta-hemolytic streptococcal growth in respiratory cultures. Plasma exchange was started for the treatment of the cytokine storm. Septic shock required vasopressors while blood cultures grew *Staphylococcus hominis*. Acute kidney injury prompted the initiation of CRRT. Due to circuit clotting, systemic heparin was initiated. Repeat respiratory culture grew ESBL *E. coli* and *Pseudomonas aeruginosa* and she was started on meropenem. She required proning and paralytics while on ventilator support. During a dialysis session, she developed paroxysmal atrial fibrillation which resolved after initiating amiodarone. On day 17, the patient had a sudden right-sided clonic seizure episode. Glasgow Coma Score remained 3 despite being off sedation for over 10 days. A head CT revealed bilateral new multifocal right front parietal and left parietal lobe infarcts, the majority of which was within right MCA territory distribution, the contralateral left parietal lesions showed evidence of hemorrhagic transformation without mass effect near the vertex. PTT at the time of bleeding was above 139 seconds.

Results

79 adult patients were admitted to the ICU, during April and May 2020, for COVID-19 related illness. 31 out of the 79 patients were on intermediate or full-dose anticoagulation. 16 of the 31 patients were on intermediate-dose anticoagulation while 15 were on full-dose anticoagulation. All patients on intermediate-dose anticoagulation were on it for the COVID-19 related hypercoagulable state, (as evidenced by elevated d-dimer and clinical situations like clotting of dialysis circuits), and this was also the commonest reason for full-dose anticoagulation.

The other diagnoses for full-dose anticoagulation included acute coronary syndrome (4 patients), atrial fibrillation (3 patients), and previous deep vein thrombosis (1 patient)

Three of these patients were on anticoagulation for atrial fibrillation and deep vein thrombosis before admission. Out of the 31 patients on intermediate or full-dose anticoagulation, three developed intracranial hemorrhages while on anticoagulation. All three patients were female and above 40 years of age. Two of these were on heparin drip while one of them was on intermediate-dose heparin. Only one patient was on full-dose anticoagulation for non-ST-segment elevated myocardial infarction and two of them were on anticoagulation for hypercoagulable state associated with COVID-19.

The table below summarizes the patients on anticoagulation who developed ICH:

Eight patients out of the 31 patients (25.8%) on therapeutic dose anticoagulation developed bleeding for which anticoagulation had to be held or stopped.

Out of the 16 patients on intermediate-dose anticoagulation, four patients (25%) developed bleeding for which anticoagulation had to be stopped. One of them developed ICH, one developed hemoptysis, the third one had evidence of upper GI bleed and the fourth one had hematuria.

Out of the 15 patients on full-dose anticoagulation, four patients (26.7%) developed bleeding for which anticoagulation had to be stopped. One of them had an upper GI bleed; two had ICH while the fourth had a pharyngeal bleed.

Discussion

Activation of coagulation pathways during cytokine storms can result in systemic thromboembolism, in both venous and arterial circulations posing the risk of ischemic infarctions to any organ. Examples include digital ischemia (also known as COVID toes), ischemic stroke, and pulmonary embolism [5].

	Sex	Age	Days admitted	AKI	Anticoagulation used	Indication for anticoagulation	Site of bleed	Disposition
1.	F	45	38	Yes	Heparin (intermediate dose)	Hypercoagulability	Left parietal and occipital lobes	Discharged
2.	F	62	35	Yes	Heparin drip	NSTEMI	Left cerebellum	Discharged
3.	F	67	25	Yes	Heparin drip	Hypercoagulability	Left parietal lobe (hemorrhagic conversion of stroke)	Died

Out of 79 patients admitted to our intensive care unit for respiratory failure due to COVID-19, these 3 patients developed intracranial hemorrhage accounting for 3.8% of our ICU population with COVID-19 infection.

The location of the first patient's intracranial hemorrhage is unusual for hypertensive emergencies. Considering the d-dimer elevation at the time, the intracranial hemorrhage may have been the result of hemorrhagic transformation of an initial ischemic infarction. This may also explain the delay between the unresponsiveness and the seizure. She also did not have any history of hypertension, and to develop hypertensive emergency in the setting of COVID-19 raises the concern for renal vascular involvement and activation of the renin-angiotensin-aldosterone system, which may also be somehow implicated in the development of her acute kidney injury. In some patients with COVID-19, kidney biopsies revealed thrombotic microangiopathy, suggesting microvascular occlusive nephropathy [6,7].

Although the second patient's intracranial hemorrhage is likely due to supratherapeutic heparin, the bradycardia and troponin elevation were likely due to COVID-19 which triggered the initiation of anticoagulation, making COVID-19 an indirect cause of intracranial hemorrhage for this patient. Although the mechanism remains unclear, several cases of bradycardia in the setting of COVID-19 infection have been documented [8]. Currently, the American College of Cardiology only recommends testing troponin levels in COVID-19 patients if myocardial infarction is suspected on clinical grounds [9].

The third patient's hypercoagulability led to recurrent clotting of the CRRT circuit, which warranted liberal use of anticoagulation. Despite the hypercoagulability in these patients, it appears that they are more prone to anticoagulation complications than the general population due to the severity of illness with vascular endothelial dysfunction and ischemic infarcts which may be complicated by hemorrhagic conversion.

The central nervous system complications in the context of COVID-19 infection may have been brought about by severe inflammatory response, direct virus invasion, or both [10]. The dilemma of whether to be proactive with prophylactic anticoagulation versus being cautious not to precipitate hemorrhagic complications certainly is far from settled in these patients.

Two of our three patients had supratherapeutic PTT levels shortly after initiation of heparin drip. In a recent review of 33 patients with hemorrhagic stroke in anti coagulated COVID-19 patients, 15 had supratherapeutic levels as well [11]. This suggests that more caution and frequent PTT checks may be warranted in COVID-19 patients.

The high incidence of acute kidney injury in hospitalized COVID-19 patients (around 20%) makes anticoagulation risky as most agents utilized need renal adjustment [12]. Data suggest that the standard 30ml/min cutoff for eGFR cannot be generalized for all patients since low molecular weight heparin may accumulate even in patients with higher creatinine clearance [13]. Since this is comparable to aiming for a moving target, we suggest that it may be safer to avoid anticoagulants that require renal adjustment.

Finally, although empiric anticoagulation is thought to reduce 28-day mortality in COVID-19 patients with elevated d-dimer, the appropriate agent and dose, and duration of treatment remain unclear [14]. Further research is required to assess the risk versus benefit of the various anticoagulants and their dosing regimens.

Conclusion

Hypercoagulability is a common problem afflicting persons with severe COVID19 infection and brings about a burden of pulmonary embolism and cerebrovascular accidents in these patients. Hypertension in hospitalized patients with COVID-19 may be a sign of micro-occlusion affecting the renal circulation and possibly the central nervous system. However, in view of bleeding complications, appropriate recommendations for anticoagulation in the setting of COVID-19 infection remain unknown. In our experience, the bleeding takes place later in the course of the illness. The benefits of anticoagulation should be weighed against the potential risk of bleeding on a case-by-case basis. An argument can be made to consider stopping anticoagulation later in the course of the disease when the inflammatory response resolves in order to minimize bleeding complications.

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