


Is therapeutic anticoagulation improving renal outcomes in COVID-19?

Sohaib Roomi ^a, Waqas Ullah ^a, Soban Farooq^b, Rehan Saeed ^a, Shujaul Haq^a and Ammar Ali Ashfaq^a

^aDepartment of Internal Medicine, Jefferson Health Abington, Abington, PA, USA; ^bDepartment of Internal Medicine, King Edward Medical University, Lahore, Pakistan

ABSTRACT

We present three patients with COVID-19 who developed acute renal failure during hospitalization and were seen to have an improvement in their kidney function after being started on therapeutic anticoagulation with heparin (Target PTT 58–93 seconds) for varying indications (atrial fibrillation, popliteal vein thrombosis and a pulmonary embolism). Their kidney functions improved significantly following anticoagulation with a clear temporal relationship between the former and latter. Anticoagulation was held for one patient due to concern of gastrointestinal bleeding and his kidney functions worsened a day after stopping anticoagulation. D-dimer levels also improved with anticoagulation but the trend of other inflammatory markers remained unpredictable.

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1. Introduction

Emerging as a cluster of pneumonia cases in Wuhan, China, in late December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has now reached across the world. Its epicenter has shifted from China to Italy to New York in a matter of 4 months [1]. On March 11, the World Health Organization (WHO) labeled it as a pandemic. As of 26 April 2020, more than 2.5 million cases have been reported worldwide with 848,000 cases in the USA alone. Despite unprecedented efforts by researchers to understand the COVID-19, many questions remain unanswered.

It has been proposed that COVID-19 induces a prothrombotic state as evidenced by microvascular thrombi in the pulmonary and renal vasculature discovered at autopsy [2]. However, evidence remains anecdotal and no specific guidelines are forthcoming. Consequently, at present, the approach to therapeutic anticoagulation varies from institution to institution. Here we describe a series of three COVID-19 patients who were admitted to the medical intensive care unit (ICU) for varying reasons and eventually received therapeutic anticoagulation for different indications. In all three, there was a temporal relationship between the onset of systemic anticoagulation and improvement of renal function. We hypothesize that anticoagulation may have helped improve kidney perfusion by relieving the microvascular clot burden.

2. Case 1

A 59-year-old man with a past medical history of hypertension and obesity (BMI 31) presented to the emergency room (ER) with fever, dry cough, dyspnea, and myalgias for the past 3 days after getting exposed to his mother at a nursing home who tested positive for COVID-19 later. On presentation, he denied chest pain, nausea, vomiting or abdominal pain. In the ER, his vitals were as follows: temperature 101.9 F, blood pressure (BP) 130/75 mmHg, heart rate 96 bpm, respiratory rate 23/min and oxygen saturation 93% on 2 liters supplemental oxygen via nasal cannula. Examination revealed diffuse bilateral bibasilar rales and with an otherwise benign exam. Chest computed tomography (CT) at presentation revealed bilateral peripheral, subpleural, ground glass opacities (Figure 1). Pertinent laboratory findings on admission and during the hospital stay are described in the table in chronological order (Table 1). During the hospitalization, the patient's oxygen requirements increased, and mentation worsened eventually necessitating intubation and transfer to the ICU. He received hydroxychloroquine, furosemide, enoxaparin for DVT prophylaxis as well as sedatives as per hospital protocol for ventilator dependant patients. He fulfilled the criteria of cytokine release syndrome with serum Ferritin > 606 mcg/L, Lymphopenia = 480 cells/ml and D-dimer level of 1803 ng/mL so he received tocilizumab as well. On Day 3 of hospitalization, he developed acute kidney injury and diuretics were held but kidney injury worsened over the next 4



Figure 1. Computed Tomography (CT) chest reveals bilateral sub-pleural ground-glass opacities.

days (Table 1). Ten days later, the patient developed atrial fibrillation with rapid ventricular response and was started on therapeutic heparin. His creatinine and BUN trended down and normalized over the following week. When heparin was held for concern of gastrointestinal bleeding, his kidney function worsened again within 24 hours. The onset of therapeutic anticoagulation immediately preceded the improvement in renal function. D-dimer levels peaked in the beginning and trended down with ongoing anticoagulation while other inflammatory markers did not reveal a predictable pattern. The patient got extubated after 3 weeks and was eventually discharged to a nursing home.

3. Case 2

A 73-year-old woman with a past medical history of insulin-dependent diabetes mellitus, chronic kidney disease (CKD) stage 3 and hypertension was brought to the ER for complaints of altered mental status and breathlessness. She was persistently hypoxic so she was intubated and started on mechanical ventilation in the ER. Her vitals were as follows: temperature 102.7 F, BP 90/55, MAP (mean arterial pressure) 66, heart rate 83 bpm, oxygen saturation 93% on pressure control ventilation with FiO₂ 85%, inspiratory pressure 19, positive end-expiratory pressure (PEEP) 12. Her labs on admission and subsequent hospital stay in the ICU are presented in Table 1. Like in case 1, she was also treated with hydroxychloroquine, tocilizumab (as she fulfilled the criteria of cytokine release syndrome), furosemide and prophylactic enoxaparin. Over the next 5 days, her oxygen requirements increased and kidney function worsened to the point that she became oliguric. On Day 6, she had swelling in her left leg and a doppler ultrasound revealed left popliteal vein thrombosis so therapeutic heparin was initiated. Over the next 4 days, her renal

function tests (RFTs) and D-dimer levels improved but her oxygen requirement remained the same (Table 1). She was palliatively extubated after discussion between the family and palliative care team, passing away in the hospital at the end of the second week.

4. Case 3

A 67-year-old male with no significant past medical history presented to the hospital with myalgias, fever and shortness of breath for the past 10 days. He tested positive for COVID-19 a week ago and was quarantined at home but symptoms progressed, prompting a visit to the ER. Vital signs on presentation were as follows: temperature 102.8, BP 110/70, heart rate 94 bpm, respiratory rate 24/min, oxygen saturation 93% on 3 liters/minute of supplemental oxygen by nasal cannula. Over the next 3 days, his respiratory symptoms worsened and he got intubated in the ICU. He developed severe acute respiratory distress syndrome (ARDS) secondary to COVID-19 and got treatment with intravenous steroids, epoprostenol and furosemide in addition to hydroxychloroquine and prophylactic lovenox as per hospital policy. One week into the ICU, the patient developed acute renal failure, worsening over the next week. On hospital day 12, the patient became hypotensive, tachycardiac and desaturated to mid-80s on the same ventilator settings. Bedside echocardiogram revealed right ventricular dilatation with akinesis of the mid free wall (Figure 2). A provisional diagnosis of Pulmonary embolism was made and the patient was started on therapeutic heparin. His kidney functions improved following the onset of systemic anticoagulation. His hospital course was complicated by health care-associated pneumonia treated with broad-spectrum antibiotics but oxygen requirement remained high. On hospital day 23, he received a tracheostomy tube and later transferred to a nursing care facility.

5. Discussion

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, positive-stranded RNA virus that attaches to angiotensin-converting enzyme 2 (ACE-2, the same receptor as SARS-CoV-1) normally present in the lungs, gastrointestinal tract and heart [3]. While a great deal remains unknown, at present it is believed that the infection spreads primarily through respiratory droplets except in case of aerosol-generating procedures [4]. About half of all people with the infection become symptomatic within 5 days, and of those that become symptomatic nearly all will have developed symptoms

Table 1. Trends in patients' labs. Days of therapeutic anticoagulation are highlighted in blue.

Patient 1	Day 1	Day 3	Day 5	Day 7	Day 9	Day 11	Day 13	Day 15	Day 17	Day 19		
Creatinine (mg/dL)	0.7	1.3	1.43	2.68	3.17	2.85	1.61	1.02	1.43	2.09		
BUN (mg/dL)	18	21	19	24	28	31	26	19	26	32		
GFR (ml/min)	>60	45	42	33	29	38	57	>60	48	32		
D-dimers (ng/mL)	965	1176	1023	1354	2163	1832	1803	1638	1926	2163		
Fibrinogen (mg/dL)	482	515	543	568	537	588	603	545	462	384		
Ferritin (ng/mL)	485	521	536	556	573	582	541	606	652	683		
CRP (mg/L)	33.5	68	139	62	89	93.7	117.8	111	54.5	27		
Patient 2	Day 1	Day 3	Day 5	Day 7	Day 9	Day 11	Day 13	Day 15	Day 17	Day 19		
Creatinine (mg/dL)	2.83	3.37	3.95	5.32	5.94	5.29	3.54		3.21			
BUN (mg/dL)	38	41	56	63	58	62	59		41			
GFR (ml/min)	52	43	26	13	16	25	39		51			
D-dimers (ng/mL)	1357	2185	2756	2842	2654	2398	2247		2047			
Fibrinogen (mg/dL)	367	157	143	158	172	264	295		184			
Ferritin (ng/mL)	683	672	696	709	682	749	721		683			
CRP (mg/L)	68	75	59	48	67	58	62	83				
Patient 3	Day 1	Day 3	Day 5	Day 7	Day 9	Day 11	Day 13	Day 15	Day 17	Day 19	Day 21	Day 23
Creatinine (mg/dL)	0.79	1.10	1.07	1.83	2.37	3.51	3.96	3.68	3.03	2.63	2.03	1.69
BUN (mg/dL)	15	11	33	47	69	81	69	53	62	46	37	31
GFR (ml/min)	>60	>60	>60	53	51	37	32	34	41	46	53	54
D-dimers (ng/mL)	742	672	789	815	731	787	823	875	891	905	836	811
Fibrinogen (mg/dL)	371	311	297	231	138	131	97	83	91	78	73	82
Ferritin (ng/mL)	459	384	371	402	472	461	421	456	489	362	397	403
CRP (mg/L)	27	44	37	31	39	35	33	37	31	37	29	21

within 12 days [5]. Clinical manifestations range from mild disease to critical illness and common symptoms are fever, cough, dyspnea, sore throat and myalgias. A small subset of patients have exhibited gastrointestinal symptoms including nausea, vomiting, diarrhea, abdominal pain and rarely dysgeusia [6]. A proposed mechanism of severe disease is misdirected innate and adaptive immunity that leads to reduced numbers of CD4 +T cells, CD8+T cells, B cells, natural killer (NK) cells, and increased neutrophil to lymphocyte ratio [7,9].

At present, no therapies have been approved for COVID-19 and a number of randomized control trials are underway. There remains an ongoing debate about the utility of therapeutic anticoagulation in COVID-19. Advocates point to the existence of widespread microvascular thrombi formation in the pulmonary and renal vasculature, which has been evidenced on autopsy studies, as playing a major role in the pathogenesis of the disease. Microvascular thrombosis is believed to cause profound hypoxia and acute kidney injury by ventilation perfusion (V/Q) mismatch in the lungs and renal vascular occlusion in the kidney, respectively. In a retrospective cohort study by Tang N from Wuhan, China a significant increase in D-dimer and prothrombin time with a decrease in fibrinogen level was associated with increased mortality [10]. Some organizations are therapeutically anticoagulating these patients based on high levels of D-dimer, abnormal coagulation parameters (coagulopathy/DIC), markedly elevated inflammatory markers (cytokine storm syndrome), and multiorgan failure. Our enterprise is currently not using therapeutic

anticoagulation unless other indications for anticoagulation exist. These three patients received anticoagulation as they developed additional complications which in themselves warranted the use of systemic heparin therapy.

Acute kidney injury (AKI) has been increasingly reported in severe COVID-19 disease but there is limited data available to estimate its true incidence and impact on the overall survival of these patients. In a single-center prospective cohort study from China based on over 700 hospitalized patients with COVID-19, AKI, proteinuria and hematuria developed in 5%, 44% and 27% of the patients, respectively, [11]. Two commonly proposed mechanisms of renal involvement in COVID-19 patients are microvascular thrombosis in renal vasculature and direct cytotoxic damage of renal vascular cells as ACE-2 enzyme is also expressed in the endothelial cells [12]. All three of our patients developed during acute renal failure during hospital stay. Limited work up was performed to rule out alternative causes of acute renal failure which included urinalysis, anti-nuclear antibodies (ANA) and retroperitoneal ultrasound. It did not reveal any alternative acute pathology. Work up was limited as it was presumed that patients with COVID-19 also develop acute kidney injury for which there is no plausible explanation at this time. First and second patients did not receive any antibiotics during hospital stay. They did receive Lasix that was held on the first day when creatinine started rising. Second patient had baseline CKD stage 3. Third patient received broad-spectrum antibiotics vancomycin, cefepime and Levofloxacin.

Vancomycin was renally dosed.

However, in all three of these patients, therapeutic anticoagulation was followed by improvement in

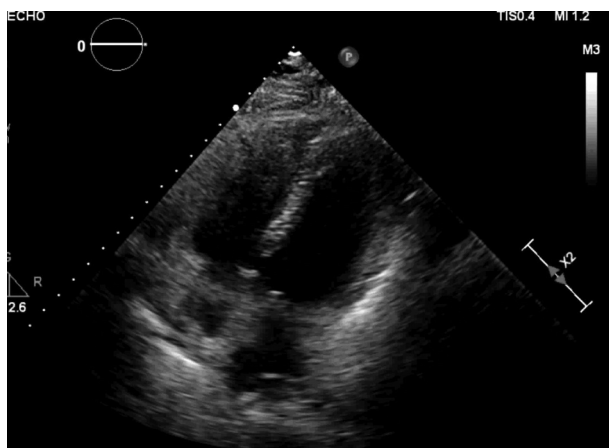


Figure 2. Apical four chamber view of Echocardiogram revealing right ventricular dilation and akinesis of the mid free wall.

renal functions and a temporal relationship is evident (Table 1). This observation was different from other patients admitted in the ICU with COVID-19 who did not receive therapeutic anticoagulation. We believe it is plausible to attribute this improvement to a reduction in the microvascular thrombi burden in the renal vasculature leading to improved renal perfusion. While we do not have vascular imaging to definitively prove that this occurred, the trend across these patients is suggestive, and perhaps future studies can further elucidate this effect. Having said this, we fully believe that this remains a grey area in the management of COVID-19 and further studies are needed before any changes to clinical practice can be considered. Therapeutic anticoagulation carries grave risks especially in already critically ill patients, and clinicians should continue to consider the risk to benefit proposition of systemic anticoagulation in the context of each individual patient.

6. Conclusion

COVID-19 increases the incidence of microvascular and macrovascular thrombotic complications. In addition to causing known complications such as deep vein thrombosis, acute coronary syndrome and pulmonary embolism, microvascular thrombosis in the renal vasculature could explain the high incidence of renal failure in this disease. We hypothesize that therapeutic anticoagulation may improve kidney function in COVID-19 patients by reducing the clot burden. More data is certainly needed to test this hypothesis and the risk and benefits of systemic anticoagulation need to be considered carefully in individual patients.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Sohaib Roomi <http://orcid.org/0000-0001-5998-9309>

Waqas Ullah <http://orcid.org/0000-0002-4850-0309>

Rehan Saeed <http://orcid.org/0000-0001-9099-4202>

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