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Tissue Plasminogen Activator (tPA) Treatment for COVID-19 Associated Acute Respiratory Distress Syndrome (ARDS): A Case Series

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CASE REPORT

Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): A case series

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Abstract

A prothrombotic coagulopathy is commonly found in critically ill COVID-19 patients with acute respiratory distress syndrome (ARDS). A unique feature of COVID-19 respiratory failure is a relatively preserved lung compliance and high Alveolar-arterial oxygen gradient, with pathology reports consistently demonstrating diffuse pulmonary microthrombi on autopsy, all consistent with a vascular occlusive etiology of respiratory failure rather than the more classic findings of low-compliance in ARDS. The COVID-19 pandemic is overwhelming the world's medical care capacity with unprecedented needs for mechanical ventilators and high rates of mortality once patients progress to needing mechanical ventilation, and in many environments including in parts of the United States the medical capacity is being exhausted. Fibrinolytic therapy has previously been used in a Phase 1 clinical trial that led to reduced mortality and marked improvements in oxygenation. Here we report a series of three patients with severe COVID-19 respiratory failure who were treated with tissue plasminogen activator. All three patients had a temporally related improvement in their respiratory status, with one of them being a durable response.

KEYWORDS

acute respiratory distress syndrome (ARDS), case report, COVID-19, fibrinolysis, tissue plasminogen activator (tPA)

Janice Wang and Negin Hajizadeh are co-first authors.

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1 | INTRODUCTION

A hallmark of severe COVID-19 is coagulopathy, with 71.4% of patients who die of COVID-19 meeting International Society on Thrombosis and Haemostasis criteria for disseminated intravascular coagulation (DIC), whereas only 0.6% of patients who survive meet these criteria.[1] Additionally, it has become clear that this is not a bleeding diathesis but rather a predominantly prothrombotic DIC with high venous thromboembolism rates, elevated D-dimer levels, high fibrinogen levels in concert with low antithrombin levels, and pulmonary congestion with microvascular thrombosis and occlusion on pathology in addition to mounting experience with high rates of central line thrombosis and vascular occlusive events (eg, ischemic limbs, strokes) observed by those who care for critically ill COVID-19 patients.[1-7] There is evidence in both animals and humans that fibrinolytic therapy in acute lung injury and acute respiratory distress syndrome (ARDS) improves survival, which also points to fibrin deposition in the pulmonary microvasculature as a contributory cause of ARDS. This would be expected to be seen in patients with ARDS and concomitant diagnoses of DIC on their laboratory values such as what is observed in more than 70% of those who die of COVID-19.[8-10] The following are three case reports of using tissue plasminogen activator (tPA) in critically ill, mechanically ventilated COVID-19 positive patients with ARDS where extracorporeal membrane oxygenation capabilities, staffing, and resources are extremely limited as a result of the current COVID-19 pandemic.

1.1 | Case 1

A 75-year-old male with a history of hypertension, hyperlipidemia, type 2 diabetes mellitus, and coronary artery disease presented to the hospital with 1 week of cough, fatigue, and fevers. Vital signs on presentation were temperature, 38.5°C; heart rate, 87 beats/min; blood pressure, 133/78 mm Hg; respiratory rate 22, oxygen saturation (SpO2) 91% on room air. Computed tomography (CT) scan of the chest revealed bilateral ground-glass opacities with peripheral and basilar predominance; COVID-19 testing was positive. Hydroxychloroquine and azithromycin were started and given for 5 days. His oxygen requirement increased from 4 to 6 L/min O2 supplementation on day of admission to 100% fraction of inspired oxygen (FiO2) on a non-rebreather mask (NRB) by day 3, with SpO2 improving from 85% to 91% with positioning in the awake prone position. Unfortunately, his severe hypoxemia persisted and he was intubated on hospital day (HD) 6 at which time his partial pressure of oxygen/FiO2 (P/F) ratio was 73. His FiO2 requirements remained >60% despite maximal ventilatory strategies, his D-dimer levels were consistently >50 000 ng/mL for the 4 days following his intubation and his fibrinogen levels ranged between 375 and 541 mg/dL. On HD 8, his P/F ratio ranged between 140 and 240 and he became anuric, for which he was initiated on continuous renal replacement therapy (CRRT); that combined with persistently elevated D-dimer, the decision was made to administer tPA (Alteplase) 25 mg intravenously over 2 hours, followed by a 25 mg tPA infusion over the subsequent 22 hours. The patient tolerated tPA therapy without bleeding or any other apparent complication. Eleven hours into his tPA infusion his P/F ratio had improved to 408, a twofold improvement from pre-tPA. Following completion of the tPA infusion, a heparin infusion was started at 10 units/kg/h with a partial thromboplastin time goal of 60 to 80. One hour into his heparin infusion, his P/F ratio worsened to 136. There was a concern for fluid overload and pulmonary edema given he was 1 L positive on his fluid balance for the prior 24 hours and remained anuric on CRRT, but efforts to remove volume via CRRT were complicated by the development of rapid atrial fibrillation and hypotension, which made it difficult to achieve a negative fluid balance. His vasopressor requirements increased from one to three (norepinephrine, phenylephrine, and vasopressin). At 48 hours post-tPA, his P/F was 188 to 250, similar to his pre-tPA status. His fibrinogen levels remained similar at 351 mg/dL and his D-dimer had decreased to 16 678 ng/mL. Unfortunately, by HD 11, the patient continued to descend into multiple organ failure with refractory hypotension secondary to arrhythmia and superimposed bacterial infection. He was made do not resuscitate and expired shortly after.

1.2 | Case 2

A 59-year-old female with a history of hypertension presented to an outside hospital after 2 days of rhinorrhea, cough, myalgias, and headaches. Vital signs from her initial presentation at the outside hospital are not available. A CT scan of the chest demonstrated bibasilar predominantly ground-glass opacities, and COVID-19 testing was positive. Hydroxychloroquine and azithromycin were initiated. Her oxygen requirement progressed over 2 days from nasal cannula O2 supplementation to 100% NRB with a partial pressure of oxygen of 137. On HD 4, she required intubation for hypoxemic respiratory failure and was transferred to our hospital. She required one vasopressor for hemodynamic support and chemical paralysis in addition to sedation. Her P/F ratio was 82 supine and improved to the 130s in the prone position. On return to supine position, her P/F ratio dropped back to as low as 90. On HD 6, her D-dimer was 545 ng/mL; this increased to 20 293 ng/mL by HD 9 with a fibrinogen level of 939 mg/dL. After 4 days of being intubated and 2 days in the prone position with no durable improvements, IV tPA (Alteplase) was administered as a 25-mg intravenous bolus over 2 hours, followed by a 25-mg tPA infusion over the subsequent 22 hours. The patient tolerated tPA therapy and was transitioned to heparin therapy (as in Case 1) without any bleeding complications. At 4 hours after completing tPA, her P/F was 135 (prone position), which was similar to pre-tPA, but by 12 hours after completing tPA, her P/F ratio had improved to 150 (prone position) with D-dimer increased to 40 490 ng/mL. By 38 hours after completing the tPA infusion, the patient continued to improve and was placed back in the supine position where the P/F ratio was now 135, a 50% improvement in

supine position P/F ratio compared with the P/F of 90 in the supine position 3 days earlier.

1.3 | Case 3

A 49-year-old male with no known medical history presented with 6 days of cough, progressive dyspnea, fever, and myalgias. Vital signs on presentation were temperature, 36.5°C; heart rate, 133 beats/min; blood pressure, 115/74 mm Hg; and a respiratory rate of 24. SpO2 was 40% on room air in the emergency department and improved to 90% on 100% FiO2 via NRB; however, given increased tachypnea, he was intubated and required one vasopressor for hemodynamic support, sedation, and chemical paralysis. A CT scan of the chest was performed and revealed bibasilar ground-glass opacities. Positive end-expiratory pressure of 20 was initially used; however, he developed pneumopericardium and thus his positive end-expiratory pressure was reduced. Hydroxychloroquine and azithromycin were started as well as heparin drip for suspicion of venous thromboembolism. On HD 1, his D-dimer was 33 228 ng/mL; on HD 2, it had reduced to 17 301 ng/mL. His P/F ratio was 120 in the prone position, and in the supine position his P/F ratio ranged from 72 to 90. His heparin drip was held and IV tPA (Alteplase) was administered similarly to as in cases 1 and 2, with the heparin drip resuming immediately after completion of the tPA infusion. His supine P/F improved from 72 to 90 pre-tPA to a P/F of 125 by 3 hours after completion of tPA, a 38% to 73% increase. There were no bleeding complications. After tPA, his D-dimer increased from 17 301 to 37 215 ng/mL and his fibrinogen decreased from 874 mg/dL (pre-tPA) to 544 mg/dL (35 hours post-tPA). By 33 hours after completing the tPA infusion, his P/F ratio declined to 71 and the patient was placed back in the prone position with recovery to a P/F ratio of 118.

2 | DISCUSSION

In summary, we now report three cases of off-label intravenous administration of tPA (Alteplase) for patients with COVID-19 suffering from ARDS and respiratory failure. In all three cases, the patients demonstrated an initial improvement in their P/F ratio, with improvements ranging from a 38% improvement (case 3) to a ~100% improvement (case 1). The observed improvements were durable in one patient but transient and lost over time in two patients after completion of their tPA infusion. In the study by Hardaway et al using fibrinolytic therapy in ARDS, they redosed the fibrinolytic agent in patients who had transient responses such as were observed in two of the three patients here, which led to more durable responses.[8] There is also precedent for using much larger bolus doses of tPA and doing so while patients remain on a therapeutic heparin drip, such as in submassive pulmonary embolism where the use of a 100-mg bolus of tPA (Alteplase) while on a therapeutic heparin drip has been shown to be highly effective in reducing mortality and only increases bleeding risk by 1.2%.[11] Such an approach using larger bolus dose tPA (50- or 100-mg bolus) without holding anticoagulation to prevent recurrence of the suspected pulmonary microvascular thrombosis underlying COVID-19 ARDS[7] is worthy of further consideration and study, and although the mortality in COVID-19 ARDS is exceptionally high, the risks of tPA must still be carefully considered given the ~1% risk of catastrophic bleeding from tPA in nonstroke patients.[11,12] Formal studies are needed to determine whether the observations in these cases were the result of tPA therapy or the result of unrelated/random effects, and (if effective) to determine the optimal dosing regimen of tPA with or without therapeutic anticoagulation in COVID-19 ARDS to include whether a redosing protocol is needed if the benefits are transient.

CONFLICT OF INTEREST

CD Barrett, HB Moore, EE Moore, and MB Yaffe have patents pending related to both coagulation/fibrinolysis diagnostics and therapeutic fibrinolytics, and are passive cofounders and hold stock options in Thrombo Therapeutics, Inc. HB Moore and EE Moore have received grant support from Haemonetics and Instrumentation Laboratories. MB Yaffe has previously received a gift of Alteplase (tPA) from Genentech, and owns stock options as a cofounder of Merrimack Pharmaceuticals. LA Veress has received grant support from Genentech. The remaining authors have nothing to disclose.

AUTHOR CONTRIBUTIONS

J Wang, N Hajizadeh, and CD Barrett prepared the manuscript with critical input and revisions from EE Moore, RC McIntyre, PK Moore, LA Veress, MB Yaffe, and HB Moore.

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