Case Report

Tissue plasminogen activator (tPA) treatment for COVID 19 associated respiratory failure: A case Series

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ABSTRACT:

The global pandemic of COVID-19 has oversaturated the medical care facilities with a large proportion of patients associated with acute respiratory distress syndrome (ARDS). ARDS in patients with COVID-19 is associated with high incidence of pulmonary embolism, pulmonary hypertension and microthrombotic complications. Although heparin is frequently used to treat thrombotic pathology COVID-19, pulmonary embolism is still observed in severe cases. Pathology reports consistently demonstrate diffuse pulmonary microthrombi on autopsy, consistent with vascular occlusive etiology of respiratory failure rather than the more classic finding in ARDS. Pulmonary microthrombi induced respiratory failure is very difficult to prove because the patients are so critically ill that transfer to CT suit to do CT pulmonary angiogram (CTPA) often become unsafe for the patients. Moreover, performing V/Q scan is increasingly difficult in these settings. Here we report a case series of 10 patients with severe COVID-19 associated respiratory failure who were treated with tissue plasminogen activator (tPA).

Keyword: COVID-19, acute respiratory distress syndrome (ARDS), Thrombolysis, Coagulopathy, Tissue plasminogen activator (tPA).

Case:

Introduction:

COVID-19 is associated with hyperinflammatory state which causes activation of coagulation cascades resulting in macro & micro thrombi in various organs. Micro thrombosis has been previously described in ARDS and viral pneumonia but appears to be more pronounced in COVID-19. Autopsy finding in lungs of COVID-19 patients are consistent with the deposition of fibrin in the airspaces and lung parenchyma, along with fibrin-platelet microthrombi in the pulmonary vasculature, which contribute to the development of progressive respiratory dysfunction and right heart failure. It has been observed that not bleeding diathesis but rather a predominantly prothrombotic Disseminated Intravascular Coagulopathy (DIC) plays a key role resulting in high venous thromboembolism, pulmonary congestion with microvascular thrombosis and vascular occlusive events (eg: Ischemic limb, Strokes).

Although activation of coagulation is linked to a systemic cytokine storm, the principal site of thrombus formation is the lungs. Reduced fibrinolysis is frequently observed in severe COVID-19 cases, and may result from high levels of plasminogen activator inhibitor (PAI)-1 release from infected, activated, necrotic endothelium and activated platelets. Patients with severe respiratory failure exhibit an abnormal pattern of gas exchange compatible with alveolar dead space ventilation and intra-pulmonary shunt (significant mixture of non-oxygenated blood with oxygenated blood).

Such anomalies strongly suggest the possibility of sudden-onset, severe pulmonary vascular involvement whose anatomical substrate would most likely be intrapulmonary disseminated acute microvascular thrombosis. The preserved lung function during the early phase of COVID-19 infection in patients with bilateral radiological opacity of the airspace suggests that pulmonary infiltrates may indeed represent areas of infarction and pulmonary hemorrhage. A pattern of hematological, biochemical, inflammatory and immune biomarkers has been identified in patients with severe pulmonary disease compared to mild systemic disease. From the analysis of published studies, hematological parameters (lymphocyte count, neutrophil/lymphocyte ratio), inflammatory (CRP, IL-6) and especially biochemical (D-dimer, troponins) that show a hypercoagulable state, have been correlated with severe prognosis and fatal outcome in COVID-19 and could, therefore, be used as prognostic markers.

The following are ten case reports using tissue plasminogen activator (tPA) in critically ill patients. All patients were treated at Asgar Ali Hospital ICU.

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Case 1:
Mr. “A” 41 years old hypertensive gentleman admitted to ICU with complaints of fever cough and increasing respiratory distress for 5 days. On presentation he was hemodynamically stable, hypoxemic with P/F ratio 165. He was diagnosed as a case of COVID-19 associated pneumonia with Type I respiratory failure and received oxygen via HFNC. As per the hospital protocol he received all supportive management including Remdesivir, Baricitinib, intravenous steroid (methylprednisolone), low molecular weight heparin (Enoxaparin) with broad spectrum antibiotic coverage. He also received Tocilizumab as his IL-6 was 86 pg/mL. On 3rd day of ICU admission patient became hypoxic with P/F ratio of 57, he was intubated and put on mechanical ventilator. Despite maximum ventilation strategy, his FiO2 remain high at 95%. His repeat D-Dimer was increased (2.6 mg/L) from normal level (0.3 mg/L) during admission. We decided to administer low dose tPA (Alteplase). Twentyfive (25 mg) tPA was administered intravenously over 2 hours, followed by 25 mg tPA infused over next 22 hours. The patient tolerated tPA therapy without bleeding or any other apparent complications. After 18 hours of completion of tPA (Alteplase) patient showed signs of improvement. His P/F ratio was improving, FiO2 was gradually lowered. He was deescalated to HFNC with FiO2 - 40%. Eventually his oxygen support was further reduced and he was able to tolerate with minimum support with 2 L O2/min through nasal prong. He was shifted to IPD on 11th day of hospital admission. By 16th day of hospital admission, he was oxygen free and on the next day he was discharged home with advice of regular follow-up.

Case 2:
A 61 years old diabetic hypertensive gentleman was admitted to the COVID unit with fever and cough for 7 days and breathing difficulties for 4 days. Initially he was on 6 lit/min oxygen via face mask. He was being treated with intravenous steroid (IV Methylprednisolone) along with Inj Remdesivir, Tab Baricitinib & LMWH (Enoxaparin) with broad spectrum antibiotic coverage. He also received Tocilizumab as his IL-6 was 86 pg/mL. On 3rd day of ICU admission patient became hypoxic with P/F ratio of 57, he was intubated and put on mechanical ventilator. Despite maximum ventilation strategy, his FiO2 remain high at 95%. His repeat D-Dimer was increased (2.6 mg/L) from normal level (0.3 mg/L) during admission. We decided to administer low dose tPA (Alteplase). Twentyfive (25 mg) tPA was administered intravenously over 2 hours, followed by 25 mg tPA infused over next 22 hours. The patient tolerated tPA therapy without bleeding or any other apparent complications. After 18 hours of completion of tPA (Alteplase) patient showed signs of improvement. His P/F ratio was improving, FiO2 was gradually lowered. He was deescalated to HFNC with FiO2 - 40%. Eventually his oxygen support was further reduced and he was able to tolerate with minimum support with 2 L O2/min through nasal prong. He was shifted to IPD on 11th day of hospital admission. By 16th day of hospital admission, he was oxygen free and on the next day he was discharged home with advice of regular follow-up.

Case 3:
Mrs. “C” 50 year’s old diabetic lady admitted to ICU with the complaints of fever and cough for 3 days and increasing respiratory distress for 2 days. She was barely able to maintain SpO2 above 90% despite giving 10 L O2/min via Face Mask on presentation. Initial HRCT chest revealed bilateral air space opacity (more on right side) with extensive involvement (around 60-70 % of total lung field). At ICU she was put on HFNC with 80% oxygen. Initial lab investigations revealed neutrophilia and lymphopenia in CBC, raised inflammatory markers, IL-6 – 127.6 pg/mL, CRP- 102 mg/L. ECG showed sinus tachycardia. Intravenous steroid was started (IV Methylprednisolone), along with Inj Remdesivir, Tab Baricitinib & LMWH (Enoxaparin). Her procalcitonin level was 0.11 ng/ml and coagulation profile were normal (PT- 10.8 sec, aPTT- 28 sec, Fibrinogen- 275.8 mg/dl). Her O2 demand was increasing and she became more restless. ABG showed severe hypoxia with P/F ratio of 61. She was intubated on 2nd day of ICU admission and was put on mechanical ventilator. We gave her 2 doses (6 mg/kg) of Tocilizumab 12 hours apart on 3rd day of ICU admission. Despite maximum ventilator adjustment she still needed high FiO2, -85% to maintain SpO2. Her D-Dimer came strongly positive (3.041 mg/L). We started tPA (Alteplase), 25 mg tPA was administered intravenously over 2 hours, followed by 25 mg tPA infused over next 22 hours on 6th day of her ICU admission. She tolerated the tPA without any complications. She showed dramatic improvement following day, her O2 requirement was decreasing. Spontaneous awakening trial (SAT) & spontaneous breathing trial (SBT) was commenced, she showed excellent tolerance. We liberated her from mechanical ventilator on 8th day of ICU admission. She was put on HFNC with FiO2 – 45%. But on 10th day her condition deteriorated rapidly. She became tachypneic, suddenly became hypoxic. She was reintubated for Type I respiratory failure. Her blood reports revealed altered coagulation profile (increased PT – 21.5 sec, aPTT- 78 sec & decreased fibrinogen -375.8 mg/dl). Her platelet count was also decreasing with 2 episodes of bleeding from CV line sites. She was diagnosed as disseminated intravascular coagulation (DIC). Along with other supportive measures after consulting with hematologist 8 U cryoprecipitate were infused to control bleeding. Her renal function also deteriorated with raising creatinine from baseline (Creatinine- 2.3 mg/dl). Despite all effort her hypoxia persists and she died on 12th day of her ICU admission.

Case 4:
Mrs. “D” 51 years old diabetic hypertensive lady admitted at the COVID unit with complaints of fever and cough for 8 days and reduced Sp02 in pulse oximeter in room air. Initially she was hemodynamically stable and required 3 lit oxygen ( P/F ratio was 267). HRCT chest showed 20% lung involvement and lab investigations revealed neutrophilia and lymphopenia in CBC, D-Dimer- 0.44 mg/L, Ferritin – 1352 ng/mL, IL-6 – 20.12 pg/mL. After admission she was prescribed with IV Remdesivir, IV steroid, Inj Enoxaparin along with other supportive measures. On 4th day of hospital admission, she
suddenly became restless and was feeling increasing shortness of breath. She was rapidly desaturating and was unable to maintain SpO₂ despite 15 L O₂/min with rebreather face mask. She was shifted to ICU (5th day of hospital admission) and was put on HFNC, required FiO₂ -95 % to maintain SpO₂ above 94%. CxR showed no new shadows. On 6th day of hospital admission the patient tolerated tPA therapy without bleeding or any other apparent complications. Her hypoxia improved dramatically (PaO₂ - 85 mmHg). FiO₂ could be lowered to 40% in HFNC. On 9th day of hospital admission (5th day of ICU admission) she was shifted back to IPD with 2 L O₂/min in Nasal Prong. She was discharged to home with adjustment of her medication on 12th day of hospital admission.

Case 5:

Mr “E” 56 year’s old diabetic hypertensive gentleman admitted at COVID unit with complaints of cough, fever and loose motion for 6 days. He was tested at home for COVID 19 RT-PCR and it came positive 2 days prior to hospital admission. Initially he was on 2 lit/min oxygen and HRCT showed 30% lung involvement (P/F ratio was 61). His initial lab investigations revealed neutrophilia and lymphopenia in CBC, D-Dimer- 0.372 mg/L, Ferritin – 985 ng/ml, IL-6 – 32.82 pg/ml. He received all supportive care including Tocilizumab as per hospital protocol. However, the patient showed no improvement rather his breathing difficulties increased. He was shifted to ICU on 8th day of hospital admission. He was hypoxic with low PaO₂ and P/F ratio of 61. on 9th day of hospital admission (2nd day of ICU admission) he was prescribed tPA (Alteplase), 25 mg tPA was administered intravenously over 2 hours, followed by 25 mg tPA infused over next 22 hours. The patient tolerated tPA therapy without any other apparent complications. From 10th day of hospital admission (3rd day of ICU admission) he showed signs of improvements. His oxygen demand could be lowered. By 12th day of hospital admission, he could now maintain his SpO₂ with 2 L O₂/min. He was shifted back to IPD (Medicine Department) as his overall wellbeing improved on 13th day of hospital admission (6th day of ICU admission). He was making gradual progress over the time. But on 17th day of hospital admission patient suddenly developed sudden respiratory distress and severe chest pain. He was shifted back to ICU. His ECG showed sinus tachycardia but his cardiac enzyme was over the roof (Troponin – 41.3 ng/ml). Patient became hemodynamically unstable and went into cardiogenic shock, requiring multiple inotropes. He developed massive pulmonary edema and unable to maintain oxygenation on NIV support. He was intubated and put on mechanical ventilator. Despite all effort we lost the patient on 17th day of hospital admission.

Case 6:

Mrs. “F” 67 year’s old lady with known case of Diabetes Mellitus, Systemic Hypertension & COPD got admitted to ICU with the complaints of fever and cough for 9 days & increasing respiratory distress for about 3 days. Upon arrival at ER, she was severely breathless, unable to complete a sentence. She had moderate wheezing with bilateral crepitation. She was supplemented with 10 L O₂/min via face mask but was barely maintained SpO₂ above 88% (P/F ratio was 65). She received all conventional treatments of COPD and COVID pneumonia. On 2nd day of ICU admission, she was prescribed with 2 doses (6 mg/kg) of Tocilizumab 12 hours apart. Patient showed minimum response. Her D-Dimer increased steeply (D-Dimer- 2.326 mg/L). Hypoxia still persist despite high O₂ support at NIV. On 4th day of ICU admission, we prescribed her tPA (Alteplase), 25 mg tPA was administered intravenously over 2 hours, followed by 25 mg tPA infused over next 22 hours. The patient tolerated tPA therapy without bleeding or any other apparent complications. 9 hours following administration she was feeling better. Her FiO₂ was lowered. On the next day (5th day of ICU admission) we could decrease her support from Bi-PAP to HFNC (FiO₂- 45%). By 8th day of ICU admission, we were able to liberate her from HFNC and was able to oxygenate her with 2 L O₂ /min via nasal prong. She was shifted to IPD under Pulmonologist on 9th day of ICU admission. Eventually she was discharged to home on 13th day of hospital admission with advice to use LTOT at home.

Case 7:

Mr. “G” 67 years old gentleman with known comorbidities of Diabetes Mellitus, Systemic Hypertension, Chronic Kidney Disease & Obstructive sleep apnea got admitted to ICU with the complaints of Fever for 8 days, Cough for 7 days with increasing breathing difficulties for last 2 days. He was obese (BMI -32) and was regularly using CPAP at home. Upon arrival at ER, he was severely dyspneic. He could barely breathe and his arterial gas showed severe hypoxia with Type II respiratory failure (P₅₀- 7.18, PaO₂ - 50 mmHg, PCO₂ - 78 mmHg, P/F ratio - 56) and was intubated and connected to mechanical ventilator. All relevant investigations done and all supportive COVID treatment was given including Tocilizumab as his IL-6 was also high. On 2nd day of ICU admission patient still required high FiO₂ despite maximum ventilator setting adjustment. CxR was disproportionately clear of consolidation or effusion. His D-Dimer level was high – 4.32 mg/L. We prescribed him tPA (Alteplase), 25 mg tPA was administered intravenously over 2 hours, followed by 25 mg tPA infused over next 22 hours. He tolerated the tPA without any complications. He showed response to tPA, his FiO₂ could be lowered. By 4th day of ICU admission, we were able to start SAT & SBT. He failed multiple attempts of breathing trial but eventually we were able to liberate him from ventilator by 7th day of ICU admission. He was put on...
HFNC with FiO₂ -45%, he also required intermittent Bi-PAP support. By 11th day of ICU admission, he tolerated O₂ therapy by Nasal Prong during day time and Bi-PAP during night time. He was transferred to IPD under Respiratory Medicine. Eventually he was shifted home with advice to use home Bi-PAP on demand with regular follow-up with Pulmonologist.

Case 8:

Mr. “H”, 54 years old gentleman with known comorbidities of COPD (Emphysematous Bullous Disease) got admitted to ICU with the complaints of fever for 8 days with breathing difficulties for 1 day. He was shifted to ICU and was put on HFNC with target range SpO₂ of 88-92%. Initial CxR showed multiple bullae, mostly in sub pleural region, some large lesions were in apical region, with consolidation on right. On query he had a history of spontaneous pneumothorax 4 month prior to this hospital admission. All initial investigations and management were given as per hospital protocol. By 4th day of ICU admission, he showed some improvement with better tolerance of HFNC with reduction in both FiO₂ and air flow. But on that night, he suddenly became severely hypoxic (PO₂ -58 mmHg, P/F ratio -144). He was put on NIV support (CPAP). CxR showed no new changes. Repeat D-Dimer was sent, which came high – 7.53 mg/L. We prescribed him tPA (Alteplase), 25 mg tPA was administered intravenously over 2 hours, followed by 25 mg tPA infused over next 22 hours. The patient tolerated tPA therapy without bleeding or any other apparent complications. He gradually showed signs of improvement. We were able to free him from CPAP and put him back to HFNC with minimum air flow. By 7th day of ICU admission, we were able to liberate him from HFNC to Nasal Prong. He was shifted to IPD with supervision of pulmonologist.

Case 9:

Mr. “I”, 71 years old gentleman with known case of Diabetes Mellitus, Systemic Hypertension, Chronic Kidney Disease & advanced Parkinson’s disease was admitted to the ICU with complaints of fever & cough for 9 days and increasing difficulties of breathing for 3 days. At ER he was severely hypoxic and was barely breathing. ABG showed severe hypoxia (PaO₂ -38 mmHg, P/F ratio- 42) with Type II respiratory failure. He was intubated immediately and shifted to ICU. We put him on mechanical ventilator. Initial lab investigations revealed neutrophilia and lymphopenia in CBC, D-Dimer- 0.556 mg/L, Ferritin – 1691 ng/ml, IL-6 – 87.43 pg/ml, CRP- 68.2 mg/dl, Procalcitonin – 0.1 ng/ml. His renal function, liver function test along with coagulation profile were within normal limit. We initiated all supportive management including intravenous steroid (methylprednisolone) and low molecular weight heparin (Enoxaparin). On 2nd day of ICU admission, we gave him 2 doses (6 mg/kg) of Tocilizumab 12 hours apart. Broad spectrum antibiotic coverage was ensured. He was still in need of high O₂ support in mechanical ventilator (FiO₂ -90% despite maximum ventilator adjustment). On 4th day of ICU admission, he was still hypoxic with high ventilator support. His D-Dimer level increased since admission (D-Dimer- 3.256 mg/L). We started tPA (Alteplase) administration. 25 mg tPA was given in bolus intravenously, and 25 mg was planned for next 22 hours. But 9 hours since infusion started patient started bleeding from multiple sites (central venous access, Urinary catheter & minor nasal bleeding). tPA stopped immediately. We cross matched and administered 8 U cryoprecipitate. Bleeding was controlled and his fibrinogen was maintaining over 200 mg /dl. His neurological exam didn’t reveal any abnormalities and CT brain on the following day was normal. Maintaining oxygenation was still very difficult despite high FiO₂ on mechanical ventilator. We put the patient on prone ventilation. But he showed little improvements. Despite every effort we lost the patient on 7th day of ICU admission.

Case 10:

Mr. “J”, 58 years old gentleman with known comorbidities of Systemic Hypertension got admitted to ICU through ER with the complaints of Fever & cough for 7 days with breathing difficulties for 2 days. At home his pulse oximetry showed decreasing pattern (<85%), while presented at ER he needed 10 L O₂/min via face mask. Initial HRCT chest showed bilateral air space opacity (more on right side), around 30-40 % of total lung field. He was admitted in ICU and put on HFNC with FiO₂ - 70%. Initial ABG showed moderate hypoxia with PaO₂ - 55 mmHg. Initial lab investigations revealed D-Dimer- 6.565 mg/L, Ferritin – 1286 ng/ml, IL-6 – 87.62 pg/ml, CRP- 128.5 mg/dl, Procalcitonin – 0.1 ng/ml. His CBC, renal function, liver function & coagulation profile were all within normal range. We prescribed him tPA (Alteplase), 25 mg tPA was administered intravenously over 2 hours, followed by 25 mg tPA infused over next 22 hours. The patient tolerated tPA therapy without bleeding or any other apparent complications. 12 hours after administration of tPA he showed signs of improvement and his FiO₂ in HFNC could be lowered. On 3rd day of ICU admission, we could liberate him from HFNC and put him on Nasal Prong, he could maintain with 2-3 L O₂/min. He was shifted on the following day at IPD under supervision of pulmonologist. Demographics, clinical characteristics at admission, treatment, and outcomes of ten patients treated with tPA (Alteplase) are summarized in Table 1. Out of 10 patient 7 were male and 3 were female. Mean age group was 57.6 years. 5 patient needed Invasive ventilator support. Rest of the 5 patients were managed with non-invasive support (2 patients by HFNC, 3 patients needed both Bi-PAP + HFNC. 6 patients presented with severe symptoms on admission with very low PaO₂/FiO₂ ratio.
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<td><strong>Treatment with tPA (Alteplase) and outcome</strong></td>
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<td>Disease duration (In days) when tPA was administered</td>
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Discussion:
Consistent findings from few autopsy series have shown significantly high incidence of pulmonary embolism and thrombotic phenomenon in patients dying due to COVID-19\textsuperscript{9-11}. Probably COVID Induced Coagulopathy (CIC) mimics presentation of pulmonary thromboembolism and pulmonary vascular shunting without hypotension initially. COVID-19 can cause severe hypercoagulable state in some patients. Mortality rates vary from 30 to 50% in critically ill patients\textsuperscript{12}. Surprisingly, very few cases of bleeding have been reported with COVID; probably coagulation pathway is significantly tilted towards hypercoagulable state rather than bleeding tendency. One study showed complete fibrinolysis shutdown, as evidenced by elevated D-Dimer and complete failure of clot lysis at 30 min on thromboelastography in critically ill patients with COVID-19\textsuperscript{13}. After learning from the autopsy findings, we changed practice at our institute and we started giving therapeutic anticoagulation to all critically ill COVID-19 patients presenting in ICU as a standard protocol. Even on therapeutic anticoagulation, some patients continue to deteriorate. So, we extrapolated low dose and ultralow dose used in MOPETT trial and The Ultra-slow PROMETEE Trial, where tPA doses of 50 mg and 25 mg were used for sub massive PE and prosthetic valve thrombosis respectively\textsuperscript{14-16}. In both the trials, efficacy was similar to conventional high dose tPA with significant low fatal bleeding rates (nil and 0.8% in MOPETT and PROMOTEE trial respectively). Several patients showed early improvement who were treated with tPA compared to other patients with COVID-19 earlier admitted in our ICU with similar grave condition. So, thrombolysis with tPA might be an attractive alternative in carefully selected individuals with rapidly deteriorating respiratory failure. Importantly, the decision of thrombolysis was always taken in consultation in interdisciplinary team after ruling out any other cause of hypoxemia. We could not get C.T. Pulmonary Angiography of these patients before thrombolysis due to poor general condition. So, there was no conventional indication of thrombolysis (like cardiogenic shock or RV dilatation) in these patients, yet after thrombolysis, we saw dramatic changes in oxygenation. This salvage therapeutic option could be decisive in patients with severe COVID-19 associated respiratory failure with no available treatment alternative.

Conclusion:
The outcome of tPA on all the 10 cases is not conclusive as there was no control group. However it will be worth to presume that patients presenting with severe symptoms of COVID-19 associate respiratory failure with low PaO\textsubscript{2}/FiO\textsubscript{2} ratio and high suspicion of pulmonary embolism, tPA (Alteplase) could be a good therapeutic option for thrombolysis.

Conflict Of Interest:
There are no conflicts of interest.

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Reference