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Review Article

Role of Tissue Plasminogen Activator (tPA) in COVID-19 Associated Respiratory Distress Syndrome: A Review of Published Case Reports

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Abstract

Background: Articles published during the COVID-19 pandemic strongly suggest the association between a hyperinflammatory state and consumptive coagulopathy pathology in critically ill COVID-19 patients. Accordingly, the use of fibrinolytic agents, in COVID-19 patients with acute respiratory distress syndrome (ARDS) would be an efficacious approach. While evidence remains limited, certain published case reports have demonstrated improvement in the PaO2/FiO2 ratio in critical patients on tPA. This warrants a literature review to understand the therapeutic effectiveness of tPA in critically ill COVID-19 patients.

Methodology: An extensive literature review on the use of tPA in critically ill COVID-19 patients using secondary sources identified 84 studies of which 42 were analyzed for further screening. Post this screening, we further narrowed our scope to a review of case reports and case series. Our analysis is based exclusively on a systematic review of 4 case reports and 5 case series concerning 24 critically ill patients showing signs and symptoms of COVID-19.

Result: Out of the 24 cases reviewed, the majority of the cases (22) developed ARDS out of which 20 patients underwent intubation followed by mechanical ventilation. The outcome was reported in terms of death (7 patients), criticality (1 patient), improvements in arterial blood gas analysis parameters (6 patients), complete clinical recovery (8 patients), and no outcome in 2 patients.

Conclusion: In this review, a majority of critically ill patients with COVID-19 showed favorable outcomes post-treatment with tPA. However, larger studies are needed to confirm these findings.

Keywords: COVID-19; SARS COV-2; Acute Respiratory Distress Syndrome; ARDS; Tissue Plasminogen Activator; tPA; rt-tPA

Introduction

The COVID-19 pandemic caused by the SARS COV-2 has impacted mankind on a global scale. It has led to a complete economic shutdown with the burden of mass morbidities and mortalities. The cause of deaths in COVID-19 patients has not been well established yet [1]. Few of the hypotheses that have been proposed pen-

dulate between adult respiratory distress syndrome (ARDS) and pulmonary micro-thrombosis mentioned as COVID induced coagulopathy (CIC) [2]. Autopsies on few deceased COVID-19 patients revealed the pulmonary endothelial injury and alveolar-capillary microthrombi [3]. A high rate of pulmonary thromboembolism has been seen in critically ill COVID 19 patients with marked elevations in D-dimer levels alone or with fibrinogen, and fibrinogen degradation products [4]. Multi-system organ dysfunction as a result of CIC has also been observed in some patients [2,5]. A literature review during the pandemic has demonstrated reduced mortality rates with anticoagulant treatment in critical patients [6]. Connecting the temporality, physicians at various centers have tried tissue plasminogen activator (tPA) is seriously ill patients with the clinical diagnosis and radiological evidence of pulmonary thrombosis. We systematically reviewed 9 articles to understand the usefulness of tPA in CIC and analyze the clinical characteristics and outcomes in critically ill patients.

Methods

We searched PubMed/Medline, Web of Science, SCOPUS, until 7th October 2020 for case reports and case series using these keywords: COVID-19, SARS-CoV-2, acute respiratory distress syndrome, ARDS, Hypoxia, Hypoxemia, Tissue plasminogen activator, tPA, rt-PA, thrombolytic. All the published case reports included in the final analysis were in English. Our search identified 84 studies in total. After removing the duplicates, there were 42 studies for further screening. After excluding the review and original articles and including only case reports and case series we found 9 articles comprised of 24 cases [1,2,7-13]. Data from the article were curated and summarized in the form of country of origin, age, and gender of the patients, their presenting complaint, any coexisting comorbidities, medical interventions during hospitalization, and their outcome. Continuous variables were presented as means ± standard deviations and categorical data as absolute values and percentages. All data extraction and descriptive analysis were performed using Microsoft Excel.

Results

A systematic analysis of 9 articles demonstrating the use of tPA in COVID patients who developed ARDS was carried out, of which 5 were written as case series and 4 were described as case reports. 24 patients who displayed diagnostic and clinical signs of ARDS in COVID positive patients were identified of the 24 cases reviewed, age ranging from 23 to 82 years (mean 52.8 years), 16 (67%) were males and 8 (33%) were females. None of the cases reported race. Most cases were reported from the United States 20 (83%) followed by India 3 (13%) and Greece 1 (4%).

The most common comorbidities reported included hypertension in 13 patients (54%), diabetes mellitus (37%) in 9 patients, hyperlipidemia in 6 patients (25%), morbid obesity in 6 patients (25%) (Table 1). The detailed list of comorbidities is mentioned in tables 1. COVID diagnosis was incidental in 6 (26%) patients; 1 ST-Elevation Myocardial Infarction(STEMI), 1 atrial fibrillation, 1 pneumopericardium, 1 neutropenia due to Acute Myeloid Leukemia (AML) management, 1 hematoma due to lupus anticoagulant, and 1 with buprenorphine withdrawal. The most common presenting symptoms were dyspnea in 13 patients (54%), fever in 10 (42%), cough in 8 (33%), generalized weakness or fatigue in 5 (21%), chest pain in 2 (8%), myalgia in 2 (8%), headache in 1 (4%), altered mental status in 1 (4%) and vomiting in 1 (4%) and signs of coagulopathy in 2 (8%). ARDS was present in 22 (92%) patients. Many patients reported more than one comorbidity and symptom. The time from the development of ARDS to the requirement of intubation in these patients varied from 1 to 14 days (median 3.5 days). Besides ARDS, acute kidney injury (AKI), as a COVID 19 complication, was present in 4 (17%) patients.

As outlined in table 2 different authors used different TPA doses and regimens. The most common dosage regimen used was 25mg over 2h followed by 25 mg continuous infusion over 22 hours in 10 (42 %) patients. Concomitant Heparin was administered in 19 patients (79%) out of which Low molecular weight heparin(LMWH) 11(46 %) and Unfractionated Heparin(UFH)8 (33%). Besides tape, the treatment (see table no. for the detailed regimes) included antimicrobial agents in addition to supportive therapy. Hydroxychloroquine (HCQ) was given in 10 patients (42%) overall; with azithromycin in 8 (33%) patients. Other agents used were penicillin or cephalosporin in 7 (29%) patients, piperacillin-tazobactam in 1 patient, and vancomycin in 1 patient. Immunosuppressive agents prescribed in these cases included tocilizumab in 2 patients and methylprednisolone in 2 patients. Convalescent plasma was administered in 2 patients. Mechanical support and vasopressors were needed in 20 (83%) and 6 (25%) patients respectively and the combination was required in patients.

Author	Age (years), Sex (M/F)	Country	Past medical history	Presenting symptoms	COVID induced Complications	Mean time from ARDS to Intubation (days)	Mechanical Support	Treatment administered
Poor., *et al*.	55 F	USA	Diabetes Mellitus, Morbid Obesity.	Not mentioned	AKI	1	VCV	HCQ, ceftriaxone
Poor., *et al*.	62 F	USA	Diabetes Mellitus, Morbid Obesity.	Not mentioned	AKI	1	VCV	Not mentioned
Poor., *et al*.	58 M	USA	Diabetes Mellitus, Morbid Obesity, HTN, COPD	Not mentioned	AKI	1	VCV	Not mentioned
Poor., *et al*.	57 M	USA	Morbid Obesity, HTN	Not mentioned	AKI	1	VCV	Convalascent Plasma
Christie., *et al*.	72 M	USA	Hyperlipidemia, HTN	Worsening SOB, Fever x7 days	Respiratory Failure	2	APRV-PCV(Day 18)	HCQ, azithromycin
Christie., *et al*.	68 F	USA	HTN, Hyperlipidemia, CVA, COPD	Worsening SOB, Altered mental status	Respiratory Failure	2	FiO2-100%/50L/min(Day3),70%/50L (Day 5)	Piperacllin tazobactum
Christie., *et al*.	55 F	USA	HTN, Hyperlipidemia, Type 2 DM, Asthama	Worsening SOB, Fever, Cough, Weakness x2.5 weeks	Respiratory Failure	3	NRB 100%	Azithromycin, augmentin, levoflox, HCQ, MPS
Christie., *et al*.	78 F	USA	Type 2 DM, CHF, HTN,CKD, CVA	Dyspnea, Fever	Respiratory Failure	1	PCV-VG with a FiO2 of 100% and PEEP of 15cmH2O.	Not mentioned
Christie., *et al*.	82 M	USA	HTN, Hyperlipidemia	Dyspnea, Cough x1 week	Respiratory Failure	3	BiPAP with a FiO2 of 100%	Not mentioned
Wang	78 M	USA	HTN, Hyperlipidemia, CAD	Cough, Fatigue, Fever x1 week	Atrial Fibrillation and Hypotension	6	None	HCQ, Azithromycin
Wang	59 F	USA	HTN	Cough, Myalgia, Headache x2 days	Buprenorphine withdrawal, Physical stress due to influenza	4	Acute respiratory distress	HCQ, Azithromycin
Wang	49 M	USA	None	Cough, Worsening SOB, Fever x6 days	Pneumopericardium	1	None	HCQ, Azithromycin

Kariyanna	68 M	USA	Lung Cancer, Asthma, STEMI	SOB, Chest Pain x2 hours	Respiratory Failure	Few days	CPR support	325 mg Aspirin, 600 mg Plavix
Molina., *et al*.	23M	USA	Nitrous Oxide abuse, Lupus Anticoagulant, Left sided neck Hematoma	Diffuse Weakness B/L LL	Coagulopathy	No ARDS	Not required	Vancomycin, cefepime, vit B12
Papamichalis	68M	Greece	HTN, DM, AML, Neutropenia	Fever x7 days	Respiratory Failure, Coagulopathy	10	APRV PEEP 8	Clarithromycin and Oseltamivir, hydroxychloquine, azithromycin, broadspectrum antibiotic (meropenem), Tocilizumab 400 mg,Convalascent Plasma Day 35
Barett., *et al*.	39M	USA	None	SOB, Chest Pain, Cough	Respiratory Failure	4	APRV PEEP16	ceftriaxone, azithromycin, hydroxychloroquine, Tocilizumab
Barett., *et al*.	58 M	USA	HTN, NIDM	SOB x2 weeks	None	14	None	ceftriaxone, azithromycin
Barett., *et al*.	67 M	USA	HTN, Thyroid Cancer	SOB, Cough, Fatigue, Fever x10 days	AKI	10	APRV FiO2 -100%	ampicillin/sulbactam, hydroxychloroquine,
Barett., *et al*.	27 M	USA	Morbid Obesity, NIDM	Cough, Fever, SOB x7days	None	7	APRV FiO2 -82%	Not mentioned
Barett., *et al*.	52M	USA	Aortic Valve Disease, Hyperlipidemia, Hodgkins Lymphoma	SOB, Fatigue, Fever, Bodyache x4 days	None	4	Not mentioned	ceftriaxone, azithromycin, hydroxychloroquine
Goyal., *et al*.	45M	India	DM	Worsening Dyspnea	None	Not applicable	FiO2-0.7	Low molecular weight heparin (LMWH)
Goyal., *et al*.	60F	India	CAD, HTN	SOB, Vomiting x4 days	None	Not applicable	FiO2-0.75	SPO2-52%
Goyal., *et al*.	59F	India	Hypothyroidism	SOB, Fever x2 days	None	Not applicable	FiO2-0.7	Not mentioned
Sethi., *et al*.	44M	USA	DM, Obesity	SOB, Cough	hypoxemic respiratory failure	Not applicable	FiO2-86%	methylprednisolone

Table 1: Demographics, Co-morbidities, Symptoms, Complications and Treatment in COVID Patients.

Author	TPA regimen	O2 requirements pre TPA infusion	O2 requirements post TPA	ABG findings pre TPA	ABG findings post TPA transfusion	Vasopressor requirement pre TPA infusion	Vasopressor requirement Post TPA transfusion	D-dimer/Fibrinogen pre TPA transfusion	D-dimer/Fibrinogen post TPA transfusion	Outcome
Poor., *et al*.	50mg over 2h fd by 2mg/h for 24h	FiO2-60% PEEP-15	Not mentioned	pH -7.12/ PaCO2-71/ PaO2-45	pH 7.27/PaCO2 40 mmHg, PaO2 78 mmHg.	norepinephrine 30 mcg/min and vasopressin 2.4 units/h	norepinephrine 4 mcg/min	5.7µg/mL	Not mentioned	Death d/t Septic Shock
Poor., *et al*.	50mg over 2h	FiO2-70% PEEP-15	Not mentioned	pH 7.33, PaCO2 55 mm Hg, and PaO2 115 mm Hg	pH 7.33, PaCO2 55 mm Hg, and PaO2 115 mm Hg	norepinephrine 15 mcg/min	Not required	6.1µg/mL	Not mentioned	Recovery 10 days
Poor., *et al*.	50mg over 75min	FiO2-60%PEEP-5	Not mentioned	pH 7.14, PaCO2 107 mm Hg and PaO2 84 mm Hg	pH 7.18, PaCO2 89 mm Hg, and PaO2 66 mm Hg,	norepinephrine 50 mcg/min and vasopressin 2.4 units/h.	norepinephrine dose was weaned to 7 mcg/min	4.6 µg/mL	Not mentioned	Death / ECHO s/o biventricular thrombi
Poor., *et al*.	50mg over 2h fd by 2mg/h	FiO2-100% PEEP-16	Not mentioned	pH 7.21, PaCO2 51 mm Hg, PO2 81 mm Hg	pH 7.27, PaCO2 51 mm Hg, and PaO2 140 mm Hg	norepinephrine 10 mcg/min	Not mentioned	6.6 µg/mL	Not mentioned	Death d/t Shock
Christie., *et al*.	25mg over 2h fd by 25 mg continuous infusion over 22 hours	Day 1 50% venturi mask, Day 2 high flow nasal cannula (HFNC) 60%/40L/min, 100%/60L/min	FiO2 of 80% (Day 11)	PaO2 53 mm Hg, PaO2/FiO2 (P/F) ratio ranging from 69 (Day 10)	P/F ratio increased to 76 (Day 11), P/F ratio -121 (Day 15), P/F ratio -127	Not required	Not required	D -dimer- 2.16ug/mL and Fibrinogen -654mg/dL	D-dimer to 9.57ug/mL (Day 11) D dimer 1.99ug/mL.	Recovery Day 18
Christie., *et al*.	25mg over 2h fd by 25 mg continuous infusion over 22 hours	100% non-rebreather (NRB), HFNC 60%/30L/min (Day 2), 100%/70L/min (Day 3)	45%40L/min (Day 4)	PaO2-72 mm Hg,	SpO2 increased from 71% to 89%	Not required	Not required	D-dimer fibrinogen were elevated at 1.87ug/mL and 512mg/dL	D-dimer initially increased to 5.57ug/mL and her fibrinogen decreased to 475mg/dL, D-dimer had decreased to 2.39ug/mL (Day 5)	Aspiration Pneumonia

Christie., *et al*.	25mg over 2h fd by 25 mg continuous infusion over 22 hours	NRB 100% (Day 4)	NRB 100% (Day 6),6L Nasal Cannula (Day 8)	PaO2 of 51mmHg (Day 1), PaO2 of 67mmHg (Day 4), PaO2 59mmHg (Day 5)	PaO2 72mmHg (Day 6), PaO2 77mmHg (Day 7)	Not required	Not required	D-dimer of 8.34ug/mL and fibrinogen of 899mg/dL	D-dimer increased to >20ug/mL, and her fibrinogen decreased to 535mg/dL (Day 6),D-dimer stayed above 20ug/m (Day 7),r D-dimer decreased to 4.56ug/mL (Day 8), D-dimer at this point was 1.91ug/mL (Day 11)	Recovery Day 13
Christie., *et al*.	25mg over 2h fd by 25 mg continuous infusion over 22 hours	NRB 100%/15L/min (Day 1), HFNC 100%/70L/min (Day 3)	FiO2 requirement was decreased from 100% to 45%	PaO2 of 48mmHg and SpO2 85% (Day 1), PaO2 of 61mmHg (Day 3)	P/F ratios ranged from 175 to 196 (Day 4), P/F ratios in the 190s (Day 5)	Required	Weaned off	D-dimer and fibrinogen were 2.47ug/mL and 744mg/dL (Day 3)	D-dimer increased to 7.05ug/mL and her fibrinogen decreased to 596mg/dL	Recovery Day 10
Christie., *et al*.	25mg over 2h fd by 25 mg continuous infusion over 22 hours	NRB 100% (Day 1), HFNC 100%/50L/min (Day 2), HFNC 100%/50L/min (Day 3)	HFNC 100%60L/min (Day 4)	PaO2 of 55mmHg and a SpO2 of 92% (Day 1), PaO2 of 57mmHg (Day 2), PaO2 of 67 mm Hg (Day 2)	PaO2 of 57mmHg (Day 3), PaO2 increased to 79mmHg (Day 3)	Not required	Not required	D-dimer and fibrinogen were 4.78ug/mL and 753mg/dL	D-dimer had increased to >20ug/mL and her fibrinogen had decreased to 693mg/dL (Day 3), D-dimer decreased to 14.06ug/mL (Day4)	Recovery Day 4
Wang., *et al*.	25mg over 2h fd by 25mg over 22h	oxygen requirement 4 to 6 L/min (Day 1), 100% fraction of inspired oxygen (FiO2) on a non-rebreather mask (NRB) by day 3	FiO2 >60%	(P/F) ratio was 73 (Day 6), P/F ratio between 140 and 240 (Day8)	P/F ratio had improved to 408 (Day 9). P/f ratio worsened to 136 (1 Hour post heparin infusion), P/F ratio- 188-250 (Day 10)	norepinephrine	Norepinephrine, Vasopressin and Phenylephrine	D-dimer >50 000 ng/mL and fibrinogen levels ranged between 375 and 541 mg/dL (Day 6-10)	Fibrinogen levels remained similar at 351 mg/dL and his D-dimer had decreased to 16 678 ng/	Death (Day 11)

Wang., *et al.*	25mg over 2h fd by 25mg over 22h	100% NRB (Day 2)	100%NRB	P/F ratio 82 (Day 4)	P/F was 135 (4 hours post transfusion) P/F ratio had improved to 150 (12 hours post transfusion), P/F ratio was now 135 (38 hours post transfusion)	None	Reduced	r D-dimer was 545 ng/mL, increased to 20 293 ng/mL by HD 9 with a fibrinogen level of 939 mg/dL	D-dimer increased to 40 490 ng/mL (12 hours post transfusion)	Improvement in P/F ratio
Wang., *et al.*	25mg over 2h fd by 25mg over 22h	100% FiO2 via NRB (Day 1)	100%FiO2	P/F ratio was 120 (prone Day 1), P/F ratio ranged from 72 to 90 (supine Day 1)	P/F of 125 by 3 hours after completion of tPA,s P/F ratio declined to 71 (supine 33 hours post Tpa), P/F ratio of 118 (prone)	Required	NA	D-dimer was 33 228 ng/ mL (Day 1) it had reduced to 17 301 ng/ml (Day 2)	D-dimer 37 215 ng/mL and his fibrinogen 544 mg/ dL (35 hours post-tPA)	Improvement in P/F ratio
Kariyanna., *et al.*	100 mg of Tpa	NA	CPR Required	PaO2 - 68.6 ph-7.29 PaCo2 -18.1 (Day 1)	PaO2-30.7 ph-7.35 PaCo2-17.5 (Day 2)	Not required	ACLS			Death (Day 2)
Molina., *et al.*	Not mentioned	SPO2-92%	None	PCO2 of 37 mmHg and a venous pH of 7.4	Not mentioned	Not required	Not required	d-dimer of 7386 ng/mL (Day 1)	Not mentioned	Not mentioned
Papamichalis	25mg over 2h fd by 25mg over 22h	Not mentioned	Not mentioned	(P/F) ratio 115 mmHg (Day 1), P/F ratio 241 mm Hg (Day 3-`10) P/F ratio 153 mmHg (Day 13)	P/F ratio 228 mmHg 15 hours after rt-PA initiation, P/F ratio <150 mm Hg 48 hours post infusion	Not required	Not required	D dimer 1.9 ng/ml (Day 1), D dimer -2.1 ng/ml (Day 3) D dimer -2.8 ng/ml (Day 6), D dimer -2.6 ng/ml (Day 8), D dimer -4.6 (Day 10), D dimer -4.9 ng/ml (Day 12)	D dimer -9.6 ng/mL (Day 13),D dimer -2.6 ng/mL (Day 35),D dimer -2.7 ng/ml (Day 45)	Death Day 45
Barett., *et al.*	25mg over 2h fd by 25mg over 22h,50 mg over 2 hrs		Not mentioned	(P/F) ratio 81 (Day 5 supine position). P/F ratio 110 (Day 5 prone position), P/F ratio 60-100 (Day 8)	P/F ratio-197 (24 hours post tpa infusion), P/F ratio - 227 (36 hours post tpa infusion)	Not required	Not required	r fibrinogen of 1,116 mg/dL, D-dimer of 7,434 ng/mL (Day 5), Fibrinogen -731mg/dl	Fibrinogen -628mg/dl	
Barett., *et al.*	50 mg over 2 hrs x2	100%FiO2 via NRB (Day 1),	Not mentioned	h P/F ratios persistently in the 90's (Day 5)	P/F ratio-136 (24 hours post tpa infusion), P/F ratio post second bolus - 90, P/F ratio -114,175	Not required	Not required	fibrinogen of 482 mg/dL (Day 1), D-dimer of 1,462 ng/mL (Day 1), pre-t PA fibrinogen was 980 mg/ dL D-dimer 2,124 ng/mL (Day 5)	, post-tPA fibrinogen 944 mg/dL , Ddimer 7,094 ng/mL	Improvement in P/F ratio

Barett., *et al.*	50 mg over 2 hrs x3	Spo2-80% (on admission), FiO2 -80%	Fi02 -50%	P/F ratios ranging from 70-105, (pH 7.1-7.2) (Day 6), P/F ratio -77 (Day 16)	P/F ratio -92 (4 hours post tpa infusion), P/F ratio -85 (24 hours post tpa infusion), P/F ratio -105 (3 hours post second infusion)	Required	Required	fibrinogen 257 mg/dL, D-dimer 6,070 ng/mL (on admission), D dimer>35,000ng/mL (Day 6)	Not mentioned	Death (Day 18)
Barett., *et al.*	50 mg over 2 hrs, 25mg over 22h,	SpO2-80% on FiO2-100% NRB (on admission)	FiO2-100% PEEP-15	P/F ratios in the 60's (prone positioning),	P/F ratio was 217 (5 hours post tpa infusion), P/F ratio - 71 (completion of infusion)	Not mentioned	Not mentioned	fibrinogen 750 mg/dL, D-dimer 2,240 ng/Ml (Day 1), (peak 856 mg/dL on HD 2 and 4), pre-tPA fibrinogen was 756mg/dL and D-dimer was 4,040 ng/Ml	post-tPA fibrinogen 856 mg/dL D-dimer to >20,000 ng/mL	Critical
Barett., *et al.*	50 mg over 2 hrs	SpO2-82% 100% FiO2-100% NRB (on admission)	Not mentioned	P/F ratio of 97 (supine Day 6), P/F ratio to >100 (prone Day 6) P/F <100 (prone Day 12)	P/F ratio immediately improved from 82 pre-tPA to 105 post-tPA (Day 12), P/F ratio had improved to 141 (Day 13)	Not required	Not required	fibrinogen of 836 mg/dL (peak 1,070 mg/dL on HD4), D-dimer of 843 ng/mL (Day 1), pre-tPA fibrinogen was 365 mg/dL and D-dimer 15,061 ng/mL (Day 12)	post-tPA fibrinogen was 373 mg/dL and D-dimer17,613 ng/mL (Day 12)	Improvement in P/F ratio
Goyal., *et al.*	2mg/hr,30mg over 15hr	FiO2-0.7 (NIV)	FiO2-0.5, FiO2-0.35 (Day 6)	Not mentioned	Not mentioned	Not required	Not required	D dimer was 1350 ng/ml and fbrinogen was 670 mg/dl (Day 2)	Not mentioned	Recovery (Day 10)
Goyal., *et al.*	50 mg over 3 hr	FiO2-0.75	FiO2-0.6 (Day 2), FiO2-0.4 (Day 3), FiO2-0.21 (Day 7)	P/F ratio -90 (on admission)	Not mentioned	Not required	Not required	D-dimer and fbrinogen were 1787 ng/ml and 704 mg/dl (Day 1)	Not mentioned	Recovery (Day 13)
Goyal., *et al.*	50 mg over 3 hr	SPO2-58% on room air, FiO2-0.7HFNC	FiO2-0.35 (3 hours post transfusion)	P/F ratio was 80	FiO2-0.35	Not required	Not required	D-dimer and fbrinogen were 4583 ng/ml and 415 mg/ dl	Not mentioned	Recovery (Day 8)
Sethi., *et al.*	100 mg over 2h	FiO2-86%	Not mentioned	pH -7.14/ PaCO2-53/ PaO2-193	Not available	norepinephrine 40 mcg/min and vasopressin 2.4 units/h	Pressors support weaned off.	>20 µg/mL	Not mentioned	Improved, remain hospitalized

Table 2: TPA Regimen, Pre and Post TPA Parameters and Outcomes.

The following parameters-Arterial blood gases (ABG), oxygen requirements, vasopressor requirements, D dimer levels, and Fibrinogen degradation products (FDP) levels were reported pre and post tPA transfusion. A clinical reduction in hypoxia was seen as an improvement in P/F ratio in 5 (21%) patients; increase in PaO2 in 15(62 %) patients and improvement in D dimer and FDP levels 7(29%) and 5 (21%) patients respectively and both D dimer and FDP in 3 (13%) patients. The tPA dosing regimens were variable in the 9 articles that were reviewed. With the usage of 25mg over 2h followed by 25mg over 22h being the most commonly administered in 9 patients (38%) and 50 mg bolus in 8(33%) patients. As per the treatment outcomes reported, 8 (33%) patients showed complete clinical recovery, 6 (25%) patients reported improvement in P/F ratio, 1 (4%) patient was reported as critical and7 (29%) patients died, no outcome was reported for 2 patients.

Discussion

Autopsy studies from the Severe Acute Respiratory Syndrome (SARS) outbreak of the early 2000s caused by SARS COV-1 reported pulmonary thrombi [4,14,15]. SARS COV- 2 appears to show a similar pro-coagulable state causing gas exchange derangements and multi-organ dysfunction [1]. As stated by Goyal., *et al*. bleeding tendencies are rare in COVID 19 patients and coagulation pathway derangement are associated with a prothrombotic state [1]. Wright., *et al*. supported this hypothesis by showing an elevated D dimer level and complete failure of clot lysis at 30 minutes on thromboelastography in seriously ill COVID positive patients [16]. To counter this hypercoagulable state, tPA has been one of the treatment modalities used in critically ill COVID 19 patients.

To the best of our knowledge, this is the first review summarizing the evidence of the use of tPA in critically ill COVID 19 patients. In addition to tPA usage across studies, concomitant heparin was also prescribed in a majority of cases. Thrombolysis with tPA showed favorable clinical outcomes reported as improvements in PaO2, P/F ratio, and coagulation parameters. The use of tPA was associated with clinical improvement in 14 out of the 24 patients included in our analysis, 8 of which were described to have a clinical recovery, 6 showed improvements in oxygenation parameters. In COVID 19 induced ARDS, mortality rates reported in critically ill patients were 30-50% on High Flow Nasal Cannula (HFNC) to 80 to 90% in patients on mechanical ventilation [11]. Of the 9 studies that we included in our analysis, 8 studies considered the intervention of intubation with mechanical ventilation and the median time to intubation from ARDS was 3.5 days. The article by Goyal., *et al*. mentioned the preference of not intubate patients and using thrombolysis as an alternative [1].

Some literature suggests that there seems to be a significant role of CIC in the pathogenesis of COVID-19 induced respiratory failure [17,18], although not all autopsy studies describe similar findings [19]. If this holds, rtPA may be an efficacious drug. However, Meyer., *et al*. in their study on "Fibrinolysis for Patients with Intermediate-Risk Pulmonary Embolism" reported an increased risk of major hemorrhage and stroke [20]. Therefore, given its recognized risks in patients with lower mortality risk, the benefit to risk ratio should be carefully considered.

Limitations

There are some inherent limitations to the current review; namely, a variability in baseline characteristics and demographics of patients included in the individual case reports/series. It is difficult to generalize the outcomes from a small set of patients to a larger population owing to the limited sample size of the analyzed data and variation in tPA dosing regimens used across studies. Furthermore, demographics and baseline information cannot be used for outcomes of a larger population without a control group. Besides, inconsistency in reporting information, making it difficult to generalize these outcomes to a larger population. Furthermore, clinical case reports have a high risk of publication bias as it is expected that only positive results will be published. Besides, heterogeneity of the included studies cannot be ignored. Small sample size could hinder a robust case selection which could eventually influence the benefit to risk ratio assessment.

Conclusion

The current review of the case reports analyzed the available literature on tPA use in severely ill COVID 19 patients. The use of tPA seems to have a favorable outcome in a noticeable number of cases. However, an analysis of clinical reports cannot replace evidence provided by clinical trials. Therefore, large studies are further needed on the topic to provide robust evidence to determine the effectiveness and optimal dosing regimen.

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