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Intravenous tPA for Acute Ischemic Stroke in Patients with COVID-19

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Background/Purpose: Coronavirus disease 2019 (COVID-19) is associated with increased risk of acute ischemic stroke (AIS), however, there is a paucity of data regarding outcomes after administration of intravenous tissue plasminogen activator (IV tPA) for stroke in patients with COVID-19.

Methods: We present a multicenter case series from 9 centers in the United States of patients with acute neurological deficits consistent with AIS and COVID-19 who were treated with IV tPA.

Results: We identified 13 patients (mean age 62 (±9.8) years, 9 (69.2%) male). All received IV tPA and 3 cases also underwent mechanical thrombectomy. All patients had systemic symptoms consistent with COVID-19 at the time of admission: fever (5 patients), cough (7 patients), and dyspnea (8 patients). The median admission NIH stroke scale (NIHSS) score was 14.5 (range 3—26) and most patients (61.5%) improved at follow up (median NIHSS score 7.5, range 0—25). No systemic or symptomatic intracranial hemorrhages were seen. Stroke mechanisms included cardioembolic (3 patients), large artery atherosclerosis (2 patients), small vessel disease (1 patient), embolic stroke of undetermined source (3 patients), and cryptogenic with incomplete investigation (1 patient). Three patients were determined to have transient ischemic attacks or aborted strokes. Two out of 12 (16.6%) patients had elevated fibrinogen levels on admission (mean 262.2 ± 87.5 mg/dl), and 7 out of 11 (63.6%) patients had an elevated D-dimer level (mean 4284.6 ±3368.9 ng/ml).

Conclusions: IV tPA may be safe and efficacious in COVID-19, but larger studies are needed to validate these results.

Keywords: IV tPA—ischemic stroke—COVID-19—thrombolysis

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Received July 7, 2020; revision received July 20, 2020; accepted July 22, 2020.

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1052-3057/$ - see front matter

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https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105201

Journal of Stroke and Cerebrovascular Diseases, Vol. 29, No. 11 (November), 2020: 105201
Introduction

Preliminary reports suggest that patients with Coronavirus Disease 2019 (COVID-19) are at high risk of hematologic complications, including disseminated intravascular coagulation (DIC).1–3 Patients with COVID-19 may exhibit hemostatic abnormalities with the potential to precipitate both hemorrhagic and thromboembolic events, including mild thrombocytopenia, prolongation of both prothrombin time and international normalized ratio, and shortened activated partial thromboplastin time, and both ischemic stroke and intracerebral hemorrhage have been described in infected patients.4–7 However, limited evidence exists in the literature for management of acute stroke in COVID-19 given the concomitant risk of hemorrhage, and recommendations are based on consensus only.8

The safety and efficacy of intravenous tissue plasminogen activator (IV tPA) for acute ischemic stroke in patients with COVID-19 remain unknown.9 We present the outcomes of a multicenter series of patients with confirmed COVID-19 infection who were treated with IV tPA for suspected acute ischemic stroke.

Methods

All patients with COVID-19 who received IV tPA for acute neurological deficits between March 1, 2020 and July 1, 2020 were identified at the participating hospitals by the corresponding stroke provider at each institution. The study protocol was approved or given exemptions by local institutional review boards. All patients included were diagnosed with COVID-19 by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RT-PCR from a nasopharyngeal swab, presented with acute neurological deficits (< 24 h), received IV tPA per acute ischemic stroke American Heart Association guidelines, and underwent brain and intracranial vessel imaging.9 Laboratory values were obtained within 24 hours of admission (Table 1). Stroke mechanism was primarily defined using the TOAST classification, with some strokes classified as embolic strokes of undetermined source (ESUS).10,11

Results

Patient characteristics

A total of 13 patients were identified at 9 centers. Mean age was 62 (±9.8) years, and 9 (69.2%) were male (Table 1). Median NIH stroke scale (NIHSS) score on admission was 14.5 (range 3–26). Eleven patients were treated within the standard window (4.5 h) with mean elapsed time between last known well and IV tPA administration of 155.4 (±24.2) min. One patient was treated with IV tPA in an extended window based on MRI/CT perfusion findings (600 min). One patient had IV tPA administered beyond the standard window based on clinical decision making with the patient (280 min).

CT angiography revealed large vessel occlusion (LVO) in 8 cases (61.5%) and MRI brain confirmed acute ischemic stroke in 4 cases (30.7%). Cerebral digital subtraction angiogram was performed in 4 (30.7%) patients. Three underwent thrombectomy, achieving thrombolysis in cerebral infarction (TICI) 3 reperfusion without complications, while one patient was found to have patent large vessels after IV tPA administration. The other four patients with LVO were not considered for thrombectomy due to unfavorable anatomy with proximal vessel stenosis or had intact collateral circulation with blood flow reconstitution distal to the occlusion site.

Stroke mechanisms included cardioembolic (3 patients), large artery atherosclerosis (2 patients), small vessel disease (1 patient), ESUS (3 patients) or cryptogenic with incomplete investigation (1 patient). Three patients were determined to have transient ischemic attacks (TIAs) or aborted strokes.

Systemic symptoms of COVID-19 were present in all patients, including fever (5 patients), cough (7 patients), and dyspnea (8 patients). Two out of 12 (16.6%) patients with fibrinogen levels tested had elevated fibrinogen levels on admission (mean 262.2 ± 87.5 mg/dl), and 7 out of 11 (63.6%) patients with D-dimer levels tested had an elevated D-dimer level (mean 4284.6 ±3368.9 ng/ml).

Safety and efficacy of IV tPA

No patients had symptomatic systemic or intracranial hemorrhage. One patient developed asymptomatic petechial hemorrhage in the area of infarction noted on routine follow-up imaging at 24 h. Median NIHSS score for patients with stroke at follow-up was 7.5 (range 0–25), and 8 (61.5%) patients had an improvement in their NIHSS score of 4 points or more. All patients survived to hospital discharge however one elderly patient was discharged to hospice because of severe respiratory symptoms.

Discussion

We describe a series of patients with COVID-19 who presented from the community and received IV tPA for acute ischemic stroke. In our series, intravenous thrombolysis was not associated with symptomatic complications, and the majority of patients had clinical improvement at follow-up.

Preliminary reports found a 1% incidence of stroke among hospitalized patients with COVID-19.4,12 More recently, acute ischemic strokes have been noted in the early stages of illness, and LVO has been reported as the presenting symptom of COVID-19.1,3,13,14 Patients with COVID-19 can also present with delirium, meningoencephalitis, and fever, which may be considered stroke mimics, posing a challenge in the evaluation for thrombolysis eligibility.6,12 In 2 case series of LVO in patients with COVID-19, 45% of patients had encephalopathy at admission, suggesting that reduced level of consciousness could
| Table 1. Clinical characteristics of patients with acute neurological deficits and COVID-19 |
|---------------------------------------------------------------|
| **Variable** | **Patient 1** | **Patient 2** | **Patient 3** | **Patient 4** | **Patient 5** | **Patient 6** | **Patient 7** | **Patient 8** | **Patient 9** | **Patient 10** |
| Age (years) | 73 | 47 | 55 | 72 | 24 | 93 | 74 | 84 | 57 | 75 |
| Sex | Male | Female | Male | Male | Male | Female | Male | Male | Male | Male |
| **Medical history and stroke risk factors** | | | | | | | | | | |
| Hypertension | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Dyslipidemia | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Smoking | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| **Medications** | None | Metformin | Olanzapine | Valproic acid | None | None | Aspirin Clopidogrel | Carvedilol | Aspirin | Amlodipine | Clonidine |
| **NIHSS score at admission** | 7 | 8 | 17 | 26 | 18 | 16 | 21 | 13 | 10 | 24 |
| **NIHSS score at 24h** | 9 | 0 | 4 | 23 | 0 | 25 (unadmitted) | N/A | 7 | 2 | 22 |
| **NIHSS score at last follow up** | 8 (day 11) | 0 (day 3) | 2 (day 12) | 16 (day 2) | 0 (day 1) | 25 (unadmitted) | N/A | 7 | 2 | 19 (day 2) |
| **Outcome status** | Discharged to rehabilitation facility | Discharged to long term acute facility | Discharged home | Discharged home | Discharged to outpatient hospice. | Discharged home | Discharged home | Discharged home (baseline neurological exam) | Discharged to rehabilitation facility | N/A |
| **Time to presentation** | 60 minutes | 100 minutes | 100 minutes | 100 minutes | 100 minutes | 113 minutes | 184 minutes | 120 minutes | 180 minutes | 600 minutes |
| **LKW to needle** | 60 minutes | 100 minutes | 100 minutes | 100 minutes | 100 minutes | 184 minutes | 120 minutes | 120 minutes | 120 minutes | 600 minutes |
| **Complications** | None | None | None | None | Asymptomatic Pneumonia | Asymptomatic Petechial Hemorrhagic Transformation | None | None | None | None |
| **Signs and symptoms of stroke** | Right facial weakness | Right hemiparesis | Right hemisensory loss | Right hemiparesis, Altered mental status | Left hemiweakness | Left hemisensory loss | Left Homonymous Hemianopia | Dysarthria | Dysarthria | Dysarthria |
| | Right hemiparesis | Right hemisensory loss | Right hemiparesis | Right hemiparesis | Right hemisensory loss | Right hemisensory loss | Right hemisensory loss | Right hemisensory loss | Right hemisensory loss | Right hemisensory loss |
| | Right hemisensory loss | Left Homonymous Hemianopia | Dysarthria | Dysarthria | Dysarthria | Dysarthria | Dysarthria | Dysarthria | Dysarthria | Dysarthria |
| | Right hemiparesis | Right hemisensory loss | Right hemiparesis | Right hemiparesis | Right hemisensory loss | Right hemisensory loss | Right hemisensory loss | Right hemisensory loss | Right hemisensory loss | Right hemisensory loss |
| Imaging | CT, CTA, MRI | CT, CTA, MRI | CT, CTA, MRI | CT, CTA, MRI | CT, CTA, MRI | CT, CTA, MRI | CT, CTA, MRI | CT, CTA, MRI | CT, CTA, MRI | CT, CTA, MRI |
| Imaging Results | CTA: Unremarkable | CTA: Unremarkable | CTA: Unremarkable | CTA: Unremarkable | CTA: Unremarkable | CTA: Unremarkable | CTA: Unremarkable | CTA: Unremarkable | CTA: Unremarkable | CTA: Unremarkable |
| Treatment for stroke | tPA | tPA | tPA | tPA | tPA | tPA and Thrombectomy | tPA and Thrombectomy | tPA and Thrombectomy | tPA and Thrombectomy | tPA |
| Covid-19 symptoms | Fever | Cough | Dyspnea | Fever | Cough | Sinusitis | Cough | Fever | Dyspnea | Cough |
| White cell count (1000/mm3) | 8.5 | 6.7 | 10.1 | 9.9 | 8.2 | 5.4 | 6.0 | 10.2 | 10.4 | 10.2 |
| Absolute Lymphocyte count (1000/mm3) | 5.2 | 1.7 | 2.4 | 0.7 | 3.1 | 0.7 | 1.4 | 1.4 | 1.5 | 1.21 |
| Platelet count (1000/mm3) | 213 | 291 | 209 | 186 | 142 | 214 | 173 | 402 | 207 | 280 |
be a common presenting symptom in patients with COVID-19-associated stroke.\textsuperscript{1,13} In our series, 61.5% patients had large vessel occlusion, but only 7% developed encephalopathy. Of note, although the Wuhan findings suggested that stroke was more common among critically ill patients, the patients in our series presented from the community with mild viral illness.\textsuperscript{7} Preliminary reports also suggest more severe illness in male patients with COVID-19, an observation that may be reflected in the male predominance of our cohort.

Growing evidence suggests SARS-CoV-2 infection is associated with a pro-thrombotic state. This process is mediated by an inflammatory cascade that leads to elevated D-dimer and fibrinogen levels, low anti-thrombin III levels and pulmonary congestion with microvascular thromboses, especially in critically ill patients.\textsuperscript{2} A clot waveform analysis study in patients with COVID-19 demonstrated that hypercoagulability preceded or coincided with severe illness.\textsuperscript{15} Anti-phospholipid antibodies have been detected in some COVID-19 patients with thromboembolic events, including those with LVOs and strokes.\textsuperscript{13,16} Our study shows a wide distribution of stroke etiologies, suggesting that COVID-19 may increase the risk for stroke through a variety of mechanisms, including those seen in other viral disorders.\textsuperscript{17} Further studies are required to elucidate stroke etiology and any causal relationship between SARS-CoV-2 infection and stroke.

IV tPA has been used anecdotally in COVID-19 to treat acute respiratory distress syndrome, but no published data exist specifically on the safety of IV tPA for acute ischemic stroke treatment.\textsuperscript{2} COVID-19 may also increase the risk of systemic or cerebral hemorrhagic complications, and has also been reported in association with acute hemorrhagic necrotizing encephalopathy.\textsuperscript{18} Our series suggests that symptomatic hemorrhagic complications with IV tPA in patients with COVID-19 are infrequent and lower than the rate of complications in the general population (between 2\% and 3.3\%), reiterating a pro-coagulable state rather than a bleeding disorder.\textsuperscript{19,20} Larger studies correlating outcomes post-thrombolysis with hemostatic measures such as d-dimer, fibrinogen levels, and thromboelastography are needed to better understand which patients are most likely to safely benefit from IV tPA administration.

Post-mortem studies have found additional evidence of fibrin-rich thrombi in patients with COVID-19, raising concern that IV tPA may be of limited benefit in this patient population in the setting of prior studies demonstrating a lower efficacy of tPA thrombolysis in thrombi with high fibrin content compared with erythrocyte-rich emboli.\textsuperscript{21,22} However, the majority of included patients had an NIHSS score improvement of 4 or more points and were discharged home, suggesting that IV tPA is efficacious in these patients. Given the small number of patients in our series, our observations should be taken with caution. The majority of patients in the study had moderate to severe
| Variable                                      | Patient 11 | Patient 12 | Patient 13 |
|----------------------------------------------|------------|------------|------------|
| **Age (years)**                              | 53         | 58         | 41         |
| **Sex**                                      | Female     | Male       | Male       |
| **Medical history and stroke risk factors**   | None       | None       | Hypertension Diabetes Heart Failure Morbid Obesity |
| **Medications**                              | None       | None       | Lisinopril Glipizide Pseudoephedrine                |
| **NIHSS score at admission**                 | 3          | 4          | 8          |
| **NIHSS score at 24h**                       | 1          | 3          | 21 (intubated) |
| **NIHSS score at last follow up**            | 3 (day 3)  | 3 (day 2)  | 19 (intubated day 24) |
| **Outcome status**                           | Home       | n/a        | n/a        |
| **Time to presentation**                     | 133 minutes| 122 minutes| 85 minutes |
| **LKW to needle**                            | 167 minutes| 280 minutes| 154 minutes|
| **Complications**                            | None       | None       | None       |
| **Signs and symptoms of stroke**             | Aphasia Right sensory loss | Aphasia Left Hemianopia | Dysarthria Right hemiparesis |
| **Imaging**                                  | CT, CTA, CTP, DSA | CT, CTA | CT, CTA |
| **Imaging Results**                          | CTA: Left Middle Cerebral artery occlusion at M1 segment | DSA: TICI III | CT: Left temporoparietal and occipital hypodensities. Right parietal hypodensity. CTA: Unremarkable |
| **Treatment for stroke**                     | tPA Thrombectomy TICI III | tPA | tPA |
| **Covid-19 symptoms**                        | Fever Dyspnea | Cough Dyspnea | None |
| **White cell count (1000/ per mm³)**         | 7.2        | 6.8        | 7.7        |
| **Absolute Lymphocyte count (1000/ per mm³)**| 2.1        | 1.0        | 3.5        |
| **Platelet count (1000/ per mm³)**           | 210        | 464        | 223        |
| **Prothrombin time (sec)**                   | 12.8       | 13.5       | 14.2       |
| **Activated partial thromboplastin time**     | 30         | 29         | 25pt       |
| **Fibrinogen (mg/dl)**                       | 265        | 132        | 266        |
| **D-dimer (ng/ml)**                          | 104        | 488        | 16,554     |
| **Ferritin (ng/ml)**                         | 65         | 446        | 740        |
| **Transthoracic echocardiogram**             | No LAE No cardiac thrombus | No LAE No cardiac thrombus | Cardiomyopathy EF 10% No cardiac thrombus |
| **Atrial Fibrillation**                      | Not detected | Not detected | Atrial tachycardias |
| **Stroke mechanism**                         | ESUS       | ESUS       | Cardiogenic   |

CT: computerized tomography  
CTA: computed tomography angiography  
CPT: CT perfusion  
CAD: coronary artery disease  
CMO: comfort measures only  
DSA: Digital subtraction angiography  
ESUS: Embolic stroke of undetermined source  
LA: Left atrium  
LAE: left atrial enlargement.  
LKW: Last known well  
LVO: Large vessel occlusion  
N/A: Not available.  
NIHSS: National Institutes of Health stroke scale  
RWA: regional wall abnormality  
SVD: Small vessel disease  
TIA: Transient ischemic attack  
TICI: Thrombolysis in cerebral infarction  
Reference ranges:  
White blood count: 4.500 to 11.000 per cubic millimeter  
Absolute lymphocytes: 1.000 to 4.800 per cubic millimeter  
Platelet count: 150.000 to 450.000 per cubic millimeter  
Prothrombin time: 12.3 to 14.9 seconds  
Activated partial-thromboplastin time: 25.4 to 34.9 seconds  
Fibrinogen: 175 to 450 mg per deciliter;  
D-dimer: 0 to 500 ng per milliliter  
Ferritin: 30 to 400 ng per milliliter
strokes (median NIHSS 14.5) and presented from the community. Therefore, our results may not be generalizable to those with mild strokes or who are critically ill.

In spite of the uncertain hematologic effects of COVID-19, our findings suggest that IV tPA may be used safely in acute ischemic stroke patients with COVID-19 and is associated with improved outcomes. Larger studies are needed to better understand safety and efficacy in this patient population.

Author contributions

Dr. Carneiro contributed with writing and reviewing of the article.
Dr. Dashkoff contributed with writing and reviewing of the article.
Dr. Leung contributed with writing and reviewing of the article.
Dr. Nobleza contributed with writing and reviewing of the article.
Dr. Marulanda-Londoño contributed with writing and reviewing of the article.
Dr. Hathidara contributed with writing and reviewing of the article.
Dr. Koch contributed with writing and reviewing of the article.
Dr. Sur contributed with writing and reviewing of the article.
Dr. Boske contributed with writing and reviewing of the article.
Dr. Voetsch contributed with writing and reviewing of the article.
Dr. Aboul Nour contributed with writing and reviewing of the article.
Dr. Miller contributed with writing and reviewing of the article.
Dr. Daneshmand contributed with writing and reviewing of the article.
Dr. Shulman contributed with writing and reviewing of the article.
Dr. Curiale contributed with writing and reviewing of the article.
Dr. Greer contributed with writing and reviewing of the article.
Dr. Romero contributed with writing and reviewing of the article.
Dr. Anand contributed with writing and reviewing of the article.
Dr. Cervantes-Arslanian contributed with writing and reviewing of the article.

Declaration of Competing Interest

None.

Acknowledgment: The authors have no acknowledgement.

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