

Catheter directed thrombolysis for COVID-19 thrombotic complications in Kurdistan-Iraq: two case reports

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Abstract

As one year elapsed since COVID-19 outbreak, venous and arterial thromboses are increasingly reported in different vascular territories. Once accessed by the virus, the endothelial cells, abundant in angiotensin converting enzyme-2 (ACE-2) protein, will be activated by the inflammatory process leading to coagulopathy and vascular lesions. Herein, we describe a case of extensive thrombosis of the infra-renal inferior vena cava and iliac femoral vein in a man of 62 and a case of acute superficial femoral artery thrombosis in a lady of 55. Both were COVID-19 confirmed cases with severe pneumonia, high D-Dimer levels and risk factors for severe disease or death. Despite presentation 1-2 weeks after the onset of thromboses, they were successfully managed by catheter directed thrombolysis (CDT) using tissue plasminogen activator (tPA). Owing to the increased morbidity and mortality of vascular thrombosis, there is a need to identify COVID-19 patients who need prophylaxis and prescribe them the right prophylactic drug (s). The excellent outcome of CDT in these two patients, from Sulaymaniyah/Iraq, supports the use of this treatment modality as a valid, safe and effective option for acute arterial and venous thromboses.

Keywords: COVID-19, arterial thrombosis, superficial femoral artery, deep vein thrombosis, inferior vena cava, iliac, femoral, percutaneous transluminal angioplasty (PTA), catheter directed thrombolysis (CDT), tissue plasminogen activator (tPA), Iraq.

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Introduction:

Novel 2019 coronavirus (COVID-19) infection was reported for the first time in December 2019. Although this viral infection usually causes a respiratory disease, varying in severity from mild symptoms to severe pneumonia, the insult of the disease is widespread. Other body organs such as the gastrointestinal tract, kidneys, heart, brain and others can be affected. Thrombotic complications are frequent and many cases of venous thromboembolisms have been described. Rare arterial thromboembolisms have also been reported mainly in the context of severe infection or in elderly patients. COVID-19 gets an access to host cells via angiotensin-converting enzyme 2 (ACE-2) protein. ACE-2 protein is abundant in the lungs, but is also expressed by endothelial cells. Activation of the inflammatory pathway in the endothelial cells may explain the increased coagulopathy and hence the vascular lesions in COVID-19 patients [1-3]. Catheter-directed thrombolysis (CDT) was defined and described for the first time by Okrent et al in a case story from 1991[4]. It is a simple technique in

which thrombolytic agents are directly delivered into the area of venous or arterial thrombosis via the use of guide wires, catheters, and delivery systems. Although CDT has been chiefly practiced for acute iliofemoral deep venous thrombosis (DVT) [5], it has applications in the arterial system as well [6]. Herein, we describe a case of extensive thrombosis of the infra-renal inferior vena cava (IVC) and iliac femoral vein in a man of 62 and a case of acute superficial femoral artery (SFA) thrombosis in a lady of 55. Both were COVID-19 confirmed cases and successfully managed by catheter directed thrombolysis (CDT). The two cases are discussed in view of the relevant literature.

Case 1

A man of 62 was admitted to Slemani Cardiac Hospital (SCH) on July 31, 2020 because of severe painful swelling of the right lower limb of 7 days' duration. Seven days earlier, he complained of sore throat, body aches, myalgia and high fever. Suspicion of COVID-19 pneumonia was confirmed by high resolution CT (HRCT) scan of the chest which showed bilateral multifocal interstitial ground glass opacities (Fig 1 A-B). The patient was a known case of hypertension for 7 years and used to smoke 2 packs per a day for many years but wasn't diabetic. He used to take valsartan 160 mg tab q.d. for hypertension.

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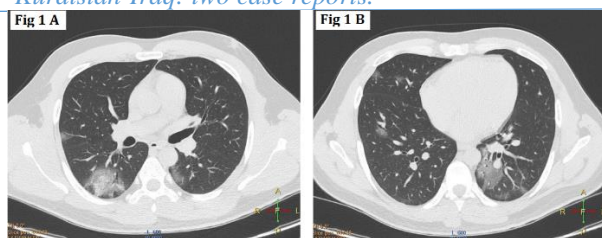


Fig 1 A-B: HRCT scan of the chest of Case 1 showing bilateral ground glass opacities consistent with covid-19 pneumonia.

On exam, the patient had a normal body built with a body mass index (BMI) of 24.8 (Body weight of 71 kg and a height of 1.69 m). The right lower limb was reddish, swollen and tender. Lab tests results were as follows: Hb=15.8 gm/dl (N: 13.8-17.2 for men and 12.1-15.1 for women), GFR=76 ml/min/1.73m² (N: ≥60), HbA1c=5.8% (N: ≤6.5%), WBC=11,000 cell/ml (N: 4,500-11,000), CRP=87 mg/L (N: <10), serum ferritin=330.7 ug/L (N: 24-336 for men and 11-307 for women), D-Dimer=766 ng/ml (N: 100-250). Duplex ultrasonography showed acute thrombosis of the infra-renal IVC and right iliac femoral vein down to the popliteal vein but there was no evidence of pulmonary embolism (PE) on HRCT scan of the chest. Oxygen was given via a nasal catheter at a flow rate of 2-3 L/minute. Moreover, aspirin 100 mg tab q.d. and Enoxaparin 6,000 IU SC b.i.d. were given since admission. However, there was neither clinical nor ultrasonic improvement in the state of deep vein thrombosis (DVT). Therefore, catheter directed thrombolysis was elected and performed as below.

1. In prone position and under sterile condition, 6-F radial sheath was inserted to the right popliteal vein with ultra-sonographic guide.
2. Venography confirmed the diagnosis of extensive DVT (Fig 2 A-C).

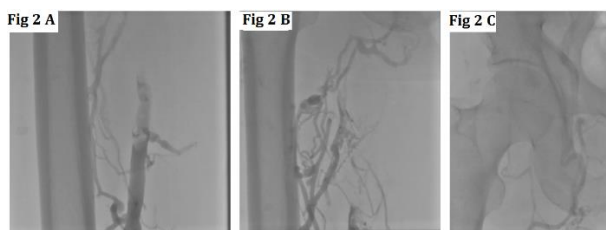


Fig 2 A-C: Baseline venography showing thrombosed femoral vein.

3. 01.8 Hi-torque command wire (Abbott Vascular) was then inserted through the sheath and passed to the level of the IVC.
4. Cragg-McNamara valved infusion catheter (ev3) was then inserted over the guide wire and through the sheath and positioned within the femoral vein (Fig 3 A-B).

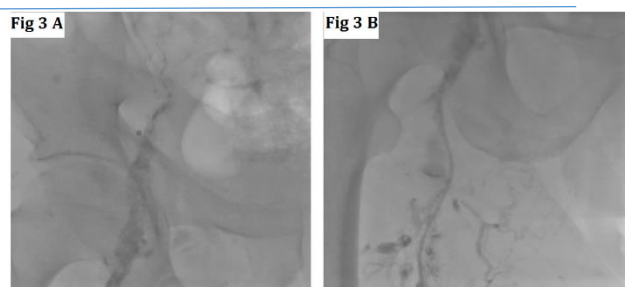


Fig 3 A-B: Perfusion catheter injection venography showing thrombosed femoral vein.

5. 5,000 IU unfractionated heparin (UFH) were then injected followed by a continuous infusion of 25,000 IU UFH in the next 24 hours.

6. A bolus of 15 mg of tissue plasminogen activator (tPA) were infused through the infusion catheter over 20 minutes followed by an infusion of 35 mg in 24 hours after which the femoral vein was well perfused as confirmed by venography (Fig 4 A-B).

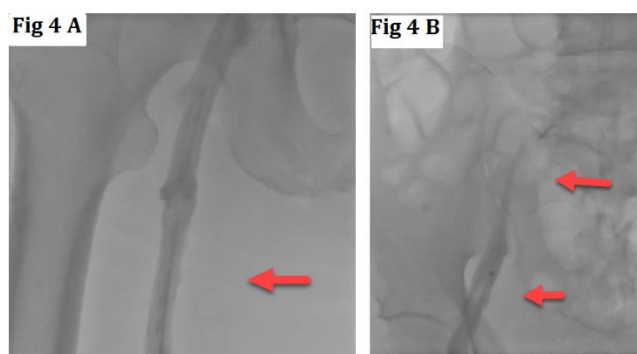


Fig 4: Venography 24 hours after bolus and infusion of 50 mg tPA showing patent right femoral vein (A) and thrombosed iliac veins (B).

7. The perfusion catheter was then advanced through the IVC to the level of the renal veins. 20 mg tPA were infused over 30 minutes followed by infusion of 30 mg tPA and 25,000 IU UFH in 24 hours after which venography showed full clot disappearance (Fig 5 A-B).

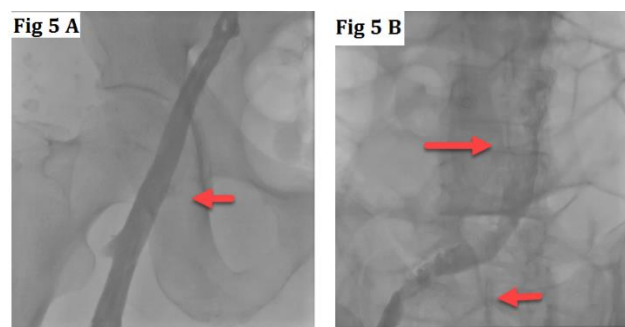


Fig 5: Venography 48 hours after bolus injection and infusion of 100 mg tPA showing patent right superficial and common femoral veins (A) and right iliac vein and IVC (B).

Case 2

A 55-years old lady was admitted to SCH on August 16, 2020 with severe pain in her right lower limb of 14 days' duration. The story began 14 days earlier when the patient developed a tingling sensation in the throat associated with high fever, body aches and abdominal pain. COVID-19 pneumonia was confirmed by HRCT of the chest which showed bilateral multifocal interstitial ground glass opacities (Fig 6 A-B). Although she was known to be insulin-dependent diabetic since 30 years ago, she never complained of lower limb ischemic pain before. She never smoked and wasn't hypertensive. While at home, the patient received azithromycin 500 mg tab q.d. for 6 days, Vit D3 5,000 IU q.d., Vit C 500 mg tab b.i.d., aspirin 100 mg tab q.d., paracetamol 1,000 mg t.i.d. and oral hypoglycemic drugs.

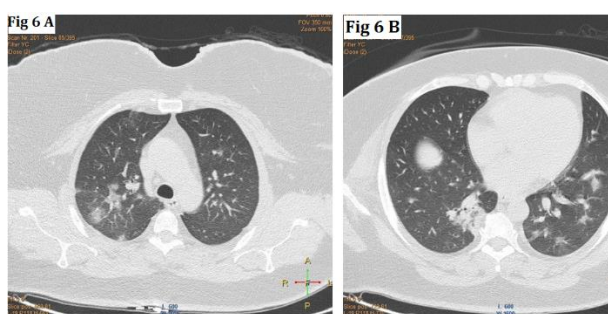


Fig 6 A-B: HRCT scan of the chest of Case 2 showing bilateral ground glass opacities consistent with covid-19 pneumonia.

On physical exam, the right lower limb was tender with absent popliteal and pedal pulses but fortunately was still viable. The patient was obese with a BMI of 30.9 (Body weight=85 kg; height=1.66 m). Lab tests results were as follows: HbA1c =9.8%, Hb=12.0 gm/dl, WBC=7,300 cell/ml, GFR=64 ml/min/1.73m², CRP= 22 mg/L, serum ferritin=197.6 ug/L and D-Dimer=1,056 ng/ml (For the normal values, please see Case 1). Duplex ultrasonography revealed acute thrombosis of the right SFA but no evidence of DVT. After admission, the oral hypoglycemic drugs were replaced by soluble insulin in a dose of 20 IU IV t.i.d. and empagliflozin 25 mg tab q.d. Moreover, she received ceftriaxone 1,000 mg IV infusion b.i.d. for 5 days and enoxaparin 6,000 IU SC b.i.d. for 3 days. Oxygen was also given via a nasal catheter at a flow rate of 2-3 L/minute. Despite the discouraging opinion of a vascular surgeon who denied embolectomy due to the "late presentation and questioned limb viability", we thought that the limb was still viable and thus deserved some sort of revascularization. Over approximately 48 hours, the patient received percutaneous transluminal angioplasty (PTA) + catheter directed thrombolysis ended in complete clearance of the thrombus. These interventions are described below:

1. In supine position and under sterile condition, diagnostic angiography was performed revealing total occlusion of the right SFA (Fig 7 A).

2. PTA was then done using an Evercross balloon (3.0*60 mm) with one minute-14 atm ballooning pressure but failed to regain arterial patency (Fig 7 B and C).

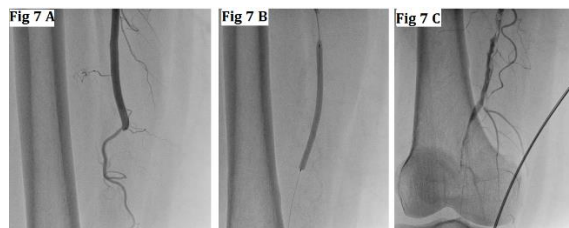


Fig 7: Baseline angiography showing a thrombus in the right SFA (A), PTA of right SFA (B) and incomplete recanalization of right SFA following PTA (C).

3. Catheter directed anti-coagulation:

- a. A 6-F femoral sheath was inserted through the left femoral artery.
- b. 01.8 Hi-torque command wire (Abbott Vascular) was then inserted through the sheath and pushed to bellow the right knee vessels (Fig 8 A).
- c. Cragg-McNamara valved infusion catheter (ev3) was then inserted over the guidewire and through the sheath with the proximal indicator placed 2 cm proximal to the occlusion (Fig 8 B).
- d. 5,000 IU UFH were then infused followed by a continuous infusion of 25,000 IU UFH in the next 24 hours (Fig 8 C).

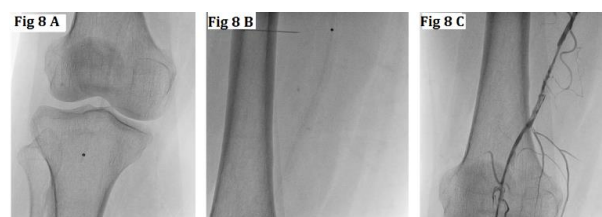


Fig 8: Distal part of perfusion catheter reached below the knee (A) while the proximal indicator is visible above the SFA thrombus (B). Injection through perfusion catheter showing big clot burden (C).

4. Catheter directed thrombolysis:

- a. A bolus of 15 mg of tPA were given through the infusion catheter over 20 minutes followed by an infusion of 35 mg in 24 hours after which the thrombus was completely dissolved as confirmed by angiography (Fig 9 A-B and Fig 10 A-B).

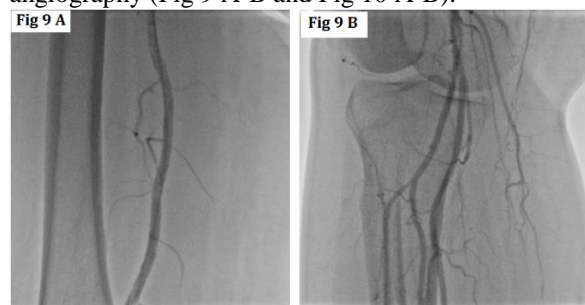


Fig 9: Angiography 24 hours post thrombolysis with tPA showing patent SFA (A) and below the knee vessels (B).

In both cases, at the end of the procedure, the perfusion catheter was removed followed by the sheath and compression pressure was applied for 20 minutes. The patients were discharged home the next day on Rivaroxaban 20 mg tab q.d. in a good general condition with complete disappearance of signs and symptoms. Rivaroxaban was prescribed for 6 months. On last follow up, both patients were fine with a normal Doppler exam.

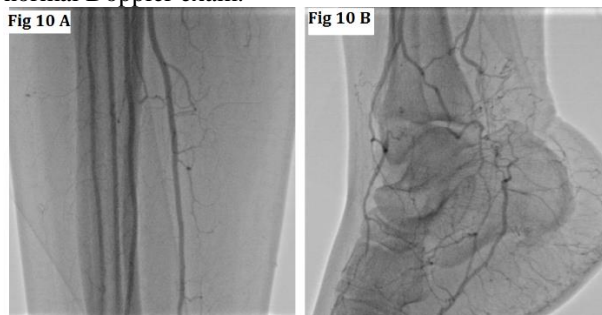


Fig 10: Angiography 24 hours post thrombolysis with tPA showing patent leg vessels (A) and foot vessels (B).

Discussion:

With the beginning of the outbreak, several series have attributed the high mortality of COVID-19 to the severe interstitial pneumonia induced by the virus. Hence, the disease was initially considered a respiratory disorder. However, the systemic nature of the disease became gradually more evident as several clinical presentations of the disease were reported. High rates of thrombotic events both for venous and arterial vessels have been described in COVID-19 patients due to endothelium activation by the inflammatory process. Moreover, COVID-19 patients could develop a large number of coagulation abnormalities including changes in the activated partial thromboplastin time (aPTT), prothrombin time (PT), and increase of D-dimer [7]. Data from coagulation analysis on admission showed higher D-dimer levels and longer prothrombin time in non-survivor COVID-19 patients than in survivors [1]. Thrombotic presentations of COVID-19 are really serious. Acute arterial thrombosis in the extremities may end in limb loss if left untreated [8] while deep venous thrombosis may lead to fatal PE. The latter may occur following a silent DVT. Despite initial believes that thrombotic complications are limited to severe pneumonia and elderly people, they have actually been reported even in the young people and non-severe cases. Arterial complications in COVID-19 take various forms. Kawasaki-like syndrome was described in children while in adults; arterial thromboembolism, acute coronary syndrome, myocardial infarction, acute aortoiliac and mesenteric arterial thrombosis, acute ischemic stroke, upper and lower limb ischemia have all been described [1]. Prevalence of thrombosis among patients with COVID-19 is not fully established. In the study of Klok et al., the cumulative incidence of a composite outcome of vascular events (acute PE, DVT, ischemic stroke, myocardial infarction, systemic arterial

embolism) among patients in the intensive care unit (ICU) was 31%, the incidence of venous thromboembolisms was 27%, and the incidence of arterial events was 3.7% [1]. Though the liability of COVID-19 patients to venous thromboembolism is widely recognized, the modes of interaction between the two diseases are still unknown. DVT, thrombophlebitis, and PE can arise irrespective of severity of pneumonia and may involve all venous regions including the pulmonary arteries. In the latter, the high number and distribution of thrombotic lesions without signs of DVT, suggest primary thrombosis rather than embolism [3]. Our first patient had no evidence of PE despite extensive DVT of the IVC and iliac femoral vein. In Iraq and many countries with unfortunately poor current health systems and resources, many people with symptoms suggestive of COVID-19 prefer to be treated at home. In such a setting, thrombotic complications of the disease may be recognized too late or not recognized at all. Moreover, the treatments taken at home are not standardized and most likely lack thrombosis prophylaxis. Consequently, the morbidity and mortality of the disease would be increased. Both patients reported in this article had COVID-19 with risk factors for severe disease or death [old age, smoking and hypertension in the first case; old age, obesity and uncontrolled diabetes mellitus (DM) in the second]. Pneumonia was severe as both patients required oxygen support. One case was treated at home for 2 weeks. LMWH was started only after admission to the hospital. D-Dimer was elevated in both cases. DVT lasted 1 week and acute arterial thrombosis of a major lower limb artery was present for 2 weeks with no response to conservative therapy until CDT was offered. The response to CDT was excellent in both cases. Patency of the iliac femoral vein and IVC was achieved in the first case and full revascularization of the entire lower limb arterial tree including the small vessels of the foot was similarly achieved in the second case. It is of interest to note, that in the second case, the limb seemed viable despite the late presentation. After 2 weeks of occlusion of SFA, it is hard to imagine that the lower limb escaped an irreversible ischemia. In our opinion, it is the gradual process of arterial thrombosis that enabled the limb to survive, possibly by the development of collaterals. Otherwise, if the limb had sustained a sudden arterial occlusion by a thromboembolic process, it would have been almost gangrenous by that time. Worthy to mention that late presentation of acutely ischemic limbs has been reported before. For instance, 30 (12%) patients in Urbak et al series had ischemic symptoms > 14 days prior to the procedure [8]. Likewise, Veyre et al reported a 24-year old COVID-19 male patient who had presented with right femoral artery thrombosis one month after the onset of pain [1]. In both cases described in this report, the procedure lasted just 48 hours with no significant morbidity and mortality. This result was similar to Urbak et al who reported a procedure time of 0-4 days with a median of 2 days [8] while Lukasiewicz et al performed an accelerated

thrombolysis over 3.5 hours [9]. During the past decades, catheter-directed thrombolysis has become part of the treatment options for acute limb ischemia in patients where primary open surgical revascularization may give suboptimal results. CDT has proven equally efficient with respect to revascularization rates and the risk of amputation and/or death. However, CDT needs time for the thrombus to dissolve, may end in incomplete revascularization and occasionally may cause cerebral hemorrhage; (0.8%) in one series [8]. CDT in our second patient could reopen the whole vasculature of the lower limb including the foot. Such a result could hardly be achieved by Fogarty arterial embolectomy catheter which is designed to remove soft, fresh emboli and thrombi from accessible arteries rather than long-standing thrombi in small arteries. To prevent venous events, prophylactic anticoagulation in high-risk situations is essential. Prevention of arterial complications, on the other hand, is more difficult. Indeed, some antiviral drugs such as ritonavir interact with certain antithrombotic treatments, making their use complicated [1]. Furthermore, the treatment of thrombosis in the setting of a deep hypercoagulable state, such as in COVID-19 patients, may be problematical in the presence of heparin resistance. The latter is a rare phenomenon in which high dose of UFH (>35,000 IU/day) is needed to achieve the target aPTT ratio [7]. The two cases described herein received LMWH SC injections and rivaroxaban tab. on admission and the latter was prescribed for 6 months after discharge from the hospital.

Conclusions:

The systemic nature of COVID-19 and the many reports of thrombosis in different arterial and venous territories entail a high index of vigilance. There is a need to identify the patients who need prophylaxis and prescribe them the right prophylactic drug (s). The excellent outcome of CDT in the two patients reported herein supports the use of this treatment modality as a valid, safe and effective option in acute arterial and venous thromboses.

Authors' Contributions:

Aram J Mirza and Abdulsalam Y Taha have equally contributed to study conception, study design, acquisition of data analysis, interpretation of data, drafting of manuscript and critical revision. Clinical management of the two reported cases was provided by Aram J Mirza.

References:

[1] Veyre F, Poulain-Veyre C, Esparcieux A, Monsarrat N, Aouifi A, Lapeze J, Chatelard P. Femoral Arterial Thrombosis in a Young Adult after Nonsevere COVID-19. *Ann Vasc Surg* 2020;28:S0890-5096(20)30604-X. doi: 10.1016/j.avsg.2020.07.013. Epub ahead of print. PMID: 32736027; PMCID: PMC7386281.

[2] Mietto C, Salice V, Ferraris M, Zuccon G, Valdambri F, Piazzalunga G et al. Acute Lower Limb Ischemia as Clinical Presentation of COVID-19 Infection. *Annals of Vascular Surgery*, 11 Aug 2020, DOI: [10.1016/j.avsg.2020.08.004](https://doi.org/10.1016/j.avsg.2020.08.004) PMID: 32791191 PMCID: PMC7417264

[3] Marone EM, Bonalumi G, Curci R, Arzini A, Chierico S, Marazzi G et al. Characteristics of Venous Thromboembolism in COVID-19 Patients: A Multicenter Experience from Northern Italy. *Ann Vasc Surg* 2020;68: 83–87 doi: 10.1016/j.avsg.2020.07.007 PMID: 32673648 PMCID: PMC7358159

[4] Okrent D, Messersmith R, Buckman J. Transcatheter fibrinolytic therapy and angioplasty for left iliofemoral venous thrombosis. *Journal of Vascular and Interventional Radiology*. 1991 May 1;2(2):195-200.

[5] Bækgaard N, Broholm R. The history of catheter-directed thrombolysis of deep venous thrombosis. *Phlebology* 2016;23(1):1-56

[6] Güneş Y, Sincer İ, Erdal E. Catheter-directed intra-arterial thrombolysis for lower extremity arterial occlusions. *Anatolian journal of cardiology*. 2019;22(2):54.

[7] Baccellieri D, Bilman V, Apruzzi L, Monaco F, D'Angelo A, Loschi D et al. A Case of Covid-19 Patient with Acute Limb Ischemia and Heparin Resistance. *Ann Vasc Surg* 2020; 68: 88–92 <https://doi.org/10.1016/j.avsg.2020.06.046>

[8] Urbak L, de la Motte L, Rørdam P, Siddiqi A, Sillesen H. Catheter-Directed Thrombolysis in the Treatment of Acute Ischemia in Lower Extremities Is Safe and Effective, Especially with Concomitant Endovascular Treatment. *Ann Vasc Dis*. 2017 Jun 25;10(2):125-131. doi: 10.3400/avd.oa.16-00140. PMID: 29034038; PMCID: PMC5579780.

[9] Lukaszewicz A, Flisinski P, Lichota W. Catheter-directed thrombolysis is not limited to acute limb ischemia treatment: experience from a division of vascular surgery. *J Cardiovasc Surg (Torino)*. 2020 Apr;61(2):200-207. doi: 10.23736/S0021-9509.17.10023-6. Epub 2017 Aug 29. PMID: 28849898.

تميع الخثرة الموجه بالقسطرة لعلاج مضاعفات COVID-19 التجلطية: تقرير عن حالتين من كردستان-العراق

د. ارام جمال مرزا
د. عبد السلام ياسين طه

الخلاصة:

مع مرور عام على تفشي مرض كوفيد-19، يتم الإبلاغ بشكل متزايد عن الخثرات الوريدية والشريانية في مناطق الأوعية الدموية المختلفة. بمجرد الإصابة بالفيروس، تؤدي العملية الالتهابية إلى تنشيط الخلايا البطانية للأوعية الدموية الحاوية على وبرة من بروتين الإنزيم المحول للأنجيوتنسين 2 (ACE-2)، وهذا بدوره يؤدي إلى اضطراب في تخثر الدم وأذيات للأوعية الدموية. في هذه المقالة، نصف حالة تجلط الدم الواسع في الوريد الأجوف السفلي تحت الكلى والوريد الحرقفي الفخذي في رجل يبلغ من العمر 62 عامًا وحالة تخثر الشريان الفخذي السطحي الحاد لدى سيدة تبلغ من العمر 55 عامًا. كلتا حالتنا كوفيد-19 مثبتة مع التهاب رئوي، ارتفاع مستويات D-Dimer ولديهما عوامل قد تقود للإصابة الشديدة وحتى الوفاة. على الرغم من وصول حالتين بعد أسبوع إلى أسبوعين من ظهور الجلطات، فقد تمت معالجتهم بنجاح عن طريق تميع الخثرة الموجه بالقسطرة (CDT) باستخدام منشط البلازمينوجين النسيجي (tPA). نظرًا لزيادة معدلات الاعتلال والوفيات الناجمة عن تجلط الدم الوعائي، هناك حاجة لتحديد مرضى كوفيد-19 الذين يحتاجون إلى الوقاية ووصف الأدوية الوقائية المناسبة لهم. تدعم النتيجة الممتازة لـ CDT في علاج هاتين الحالتين، من السليمانية / العراق، استخدام طريقة العلاج هذه كخيار صالح وآمن وفعال للتخثرات الشريانية والوريدية الحادة.

الكلمات المفتاحية

كوفيد-19، تجلط الدم الشرياني، الشريان الفخذي السطحي، تجلط الأوردة العميقة، الوريد الأجوف السفلي، الحرقفي، الفخذ، رآب الوعاء عن طريق الجلد، تحلل الخثرة الموجه بالقسطرة، منشط البلازمينوجين النسيجي، العراق.