J Rehabil Med 2020; 52: jrm00094

SPECIAL REPORT

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REHABILITATION OF COVID-19 PATIENTS WITH ACUTE LOWER EXTREMITY ISCHAEMIA AND AMPUTATION

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Objective: **To evaluate the clinical characteristics and rehabilitation management of patients who undergo amputation for COVID-19-associated coagulopathy.**

Methods: **Clinical and laboratory data for 3 patients were analysed and their rehabilitative management discussed.**

Results: **The medical records of 3 patients who had undergone amputation due to acute lower extremity ischaemia and who were provided with rehabilitation in the COVID-19 unit at San Raffaele Scientific Insitute, Milan Italy were reviewed.**

Conclusion: **Coagulation changes related to SARS-CoV-2 may complicate recovery from this devastating disease. The rehabilitation management of amputated patients for COVID-19 acute lower extremity ischaemia is based on a multilevel approach for clinical, functional, nutritional and neuropsychological needs. Based on this limited experience, a dedicated programme for this specific group of patients seems advantageous to warrant the best functional outcome and quality of life.**

Key words: COVID-19; SARS-CoV-2; amputation; COVID-19 coagulopathy; rehabilitation; ischaemia.

Accepted Jul 2, 2020; Epub ahead of Jul 16, 2020

J Rehabil Med 2020; 52: jrm00094

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LAY ABSTRACT

COVID-19 is a devastating disease, which, in addition to pulmonary manifestations, causes several syndromes. Alteration of the coagulation system leads to thrombotic sequelae, which are typically associated with severe manifestations of SARS-CoV-2. These disorders can cause acute ischaemia of the lower limbs, necessitating amputation. This study reports the rehabilitation needs of 3 patients, highlighting the importance of a multidisciplinary tailored approach. Correct evaluation of the needs of this specific group of patients is essential to improve their chances of the optimum functional outcome and quality of life.

In Italy, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in more than 230,000 positive cases, with approximately 35,000 deaths, predominately in the north of the country. Recent studies have modified the diagnostic and therapeutic approach that was taken at the start of the pandemic, particularly regarding the target organs of coronavirus disease 2019 (COVID-19). These findings have also highlighted the need for a multidisciplinary rehabilitative approach to these patients in the acute phase, as well as in the post-acute phase (1). Respiratory distress syndrome is not the only aspect of COVID-19; several other organs are directly affected, such as the heart, kidney, brain, and blood vessels, with endothelial damage, disepithelization, vasculitis, and development of micro-thrombi (1).

Patients with severe manifestation of COVID-19 have been shown to have important alteration of the coagulation cascade, such as disseminated intravascular coagulopathy (DIC) and thrombotic microangiopathy. The most common laboratory anomalies affect values of D-dimer, thrombocytopaenia, and prologned clotting time indicative for DIC, which differs from the sepsis-related DIC as it has high values of D-dimer and severe thrombocytopaenia. High levels of lactate dehydrogenase (LDH) and ferritin have also been reported, whereas autoptic surveys have showed platelet thrombotic deposits in the small vessels of the lungs and other organs (1). The physiopathology of the microvascular damage, thrombosis, and multiorgan failure caused by COVID-19 infection appears to be related to the affinity of SARS-CoV-2 for the angiotensin 2 receptor, which is thought to be the viral entry point into human cells, and is expressed in type 2 alveolar epithelial cells and endothelial cells (1–6).

So-called COVID-19-associated coagulopathy (CAC) is the array of coagulation alterations typical of infected patients (2–4, 7–10). This reflects a high prothrombotic status, which is associated with severe manifestation of the disease and increased mortality (6, 8).

Acute lower extremities ischaemia (ALI) is a severe consequence of hypercoagulability, the incidence of which is increased in patients with COVID-19 (2, 3, 9, 11). Moreover, in these cases a high incidence of

doi: 10.2340/16501977-2714

revascularization failure has been reported, probably due to excessive virus-related hypercoagulability (7, 8). The inefficacy of surgical and medical revascularization therapies and the clinical status of patients with COVID-19 leads to amputation of the affected limb. Once the patient has undergone amputation, a dedicated rehabilitation programme is then fundamental, which must take into account different and specific aspects, such as the patient's recovery after the acute phase of the infection and surgical intervention, management of pain, and preparation for the prosthesis prescription, manufacturing, fitting, and training. These aspects are all mandatory for the functional recovery of these patients and improvement in their quality of life (QoL).

The aim of this study was to review the clinical and rehabilitative findings from 3 cases of amputated COVID-19 patients who were managed in our unit, and to emphasize the importance of early rehabilitative management of these patients.

MATERIAL AND METHODS

The medical history of a series of cases that underwent rehabilitation in the COVID-19 rehabilitation unit in San Raffaele Scientific Institute, Milan, Italy were retrospectively reviewed, and their clinical and rehabilitation history discussed.

All procedures involving human participants were performed in accordance with the ethics standards of the institutional research committee and with the Declaration of Helsinki 1964 and its later amendments or comparable ethics standards. Informed consent was obtained from all participants included in the study.

RESULTS

Three patients with amputation, who underwent rehabilitation in our department since the month of April 2020, were included.

Case 1

A 58-year-old man with a history of hypertension, diabetes mellitus and hypothyroidism, underwent intubation for SARS-CoV-2. He was given hydroxychloroquine (HCQ) therapy. The patient was extubated due to improvement in his respiratory parameters after 7 days. A few days after extubation, the patient experienced progressive bilateral lower limb critical ischaemia, with necrosis of the left foot and microischaemic lesions of the right toes. Laboratory testing revealed: fibrinogen 718 mg/dl; LDH 738 U/l; and D-dimer >20 µg/ml. Platelet count, international normalized ratio (INR) and partial thromboplastin time (PTT) were normal. The patient underwent left lower limb transfemoral amputation, whereas medical therapy with low-molecular-weight heparin (LMWH), aspirin, and vasodilator agents was started for the right lower limb. The patient was then admitted to the rehabilitation unit. Therapy was started for neuropathic pain, swallowing evaluation, neurocognitive and nutritional support, together with setting an appropriate protocol for a sacral pressure injury. The residual limb was then manually prepared for prosthetic positioning and a rehabilitation programme for the improvement of functional independence was started.

Case 2

A 75-year-old man with a history of hypertension, hypertensive cardiomyopathy, diabetes mellitus, chronic kidney failure and peripheral neuropathy was admitted to the emergency unit for pain and hypothermia of the right lower limb. He had tachycardia, tachypnoea, hypoxaemia, and hypertension. Thoracic computed tomography (CT) scan revealed parenchymal thickening with a crazy paving pattern. Swab testing was positive for SARS-CoV-2. Laboratory testing revealed: fibrinogen 529 mg/dl; LDH 332 U/l. Platelet count, INR and PTT were normal.

The patient underwent antibiotic and antiviral therapy. Azithromycin (AZM); lopinavir/ritornavir, HCQ, and continuous positive airway pressure (CPAP) ventilation were started. Because of the patient's serious clinical situation and the damage to the microcirculation, no revascularization intervention was indicated and medical therapy with LMWH, aspirin, and vasodilator agents was started. Once the respiratory parameter improved, the patient underwent right transfemoral lower limb amputation with application of negative-pressure wound therapy. A few days after surgery, the patient was admitted to our rehabilitation unit. A specific rehabilitation protocol was started, to improve verticalization, postural changes and to prepare the stump for prosthetic fitting. Vacuum Assisted Closure® (V.A.C.®) therapy was continued for a small dehiscence of the surgical wound. The patients underwent swallowing evaluation, and nutritional and neuropsychological support. Neuropathic pain therapy was adjusted, and the VAC therapy was removed 10 days after admission to our unit. The patient is currently able to walk independently with a walker, and a customized temporary prosthesis is in production.

Case 3

A 70-year-old man with history of hypertension, dyslipidaemia and chronic obstructive bronchopneumonia was admitted in the emergency unit for hyperthermia and dyspnoea. COVID-19 was detected on swab testing and a chest X-ray was consistent with pneumonia. AZM, HCQ, LMWH were started, together with CPAP.

Table I. Clinical and laboratory data for 3 patients amputated due to acute lower extremities ischaemia caused by COVID-19 infection

Case number	Age, years/sex	Affected lower limb	Fibrinogen (mg/dl)	D-dimer (µg/ml)	LDH (U/l)	Ventilation type	Medical therapy	ALI medical treatment	Amputation
1	59/M	Bilateral	718	>20	738	Intubation	HCQ	Iloprost, statin, ASA, LMWH	Transfemoral (left)
2	75/M	Right	529	N/A	332	CPAP	AZM, HCQ, LPV/r	Alpostradil, LMWH	Transfemoral
3	70/M	Right	152	5.04	711	CPAP	AZ, HCQ, TCZ	ASA, LMWH	Transfemoral

LDH: lactate dehydrogenase; ALI: acute lower extremities ischaemia; CPAP: continuous positive airway pressure; AZM: azithromycin; HCQ: hydroxychloroquine; LPV/r: lopinavir/ritonavir; ASA: acetylsalicylic acid; TCZ: tocilizubam; M: male; LMWH: low molecular weight heparin.

Due to worsening respiratory parameters, tocilizumab administration was started. Five days after hospital admission, ALI was detected, with thrombosis of the vascular axis of the right lower limb, and occlusion of the superficial, deep and common femoral and popliteal arteries. Laboratory testing showed the following values: fibrinogen 152 mg/dl; LDH 711 U/l; D-dimer 5.04 µg/ml. Platelet count, INR and PTT were normal.

The patient underwent emergent endovascular embolectomy with a Fogarty catheter. Because of revascularization failure, the patient underwent transfemoral amputation of the right lower limb 2 days later. A deep venous thrombosis of the left lower limb was detected one day later. One week after surgery, the patient was admitted to our rehabilitation unit. Following multidisciplinary evaluation, the patients commenced early rehabilitation, with postural training, manual management of the stump, and a silicon sheath. The rehabilitation programme was stopped after 7 days because the patient needed surgical revision of the wound and developed pneumonia. After 10 days, the patient started a new programme and is currently improving in autonomy.

In all 3 cases reported here the patients had COVID-19 respiratory syndrome. In one case intubation was necessary, and in the other 2 cases CPAP was administered. Antibiotics were administered in 2 cases (AZM; cases 2 and 3), antiviral treatment in 1 case, immunomodulant therapy in 1 case, and in all 3 cases the patients underwent HCQ. All laboratory testing showed a hypercoagulability status, which led to amputation at the thigh. Table I summarizes the clinical and laboratory data for this case series.

DISCUSSION

SARS-CoV-2 directly affects several organs, leading to high morbidity and mortality (4). One of the main causes of morbidity is CAC, which seems to be the main cause of ALI (5). Hypercoagulability was found in all 3 cases reported here, as demonstrated by the levels of LDH, fibrinogen and D-dimer (4). Frequent amputation of patients with COVID-19 who develop ALI have also been reported, because of the higher rate of failure of revascularization techniques or medical therapies compared with non-COVID-19 cases (2, 4, 5). The rehabilitation management of COVID-19 patients with ALI is essential to improve functional autonomy and QoL. Stump management, with frequent dressing, manual mobilization treatment and analgesic therapy adjustments, are important for reconditioning the musculoskeletal system, which is compromised by the infection.

A tailored therapeutic-rehabilitation programme for these patients should focus on the recovery of functional autonomy, the disability, and on returning the patient as much as possible to social activities, in order to provide an acceptable QoL (12). A dedicated team of physiotherapists in our unit is involved in providing the individual rehabilitation programme, through maintenance of the elasticity of the residual limb, and prevention of post-operative contractures through selective training of the hamstrings, quadriceps, abductors, and adductors in the case of thigh amputation. Moreover, muscle-strengthening exercises, perceptive and coordination motor training, together with aerobic training for cardiorespiratory reconditioning and balance recovery are necessary (13).

Patients are also trained to adapt to the postural changes and recovery of verticalization. Finally, the correct mobilization aid is identified and the patient is trained in its use for the resumption of walking. In addition to physical management, patients in our unit are provided with psychological support and cognitive-behavioural therapy, which is known to reduce the anxiety and depression of this group of patients (14). Finally, amputated COVID-19 patients undergo continuous evaluation of their nutritional status, because, in optimal conditions, this improves the overall clinical status of these patients (15). Furthermore, optimal nutritional status is essential for the healing process and to prevent infections, especially for amputated patients with alterations in their microcirculation. Malnourished patients frequently develop pressure ulcers, infections, and delayed wound healing, which reduce the degree of clinical recovery and complicate the prosthesis of the stump (15–17). In our unit, we created an ad-hoc programme for amputated patients to start the processes of rehabilitation and prosthesis fitting. In most cases we positioned a postoperative silicone sheath, and thereafter a new system with a silicone suspension cap, once the stump was ready for the prosthesis (18).

In the early stage after admission to the rehabilitation unit, daily measurement is taken of the stump, 4 cm from the edge of the wound, and the patient wears a 3-mm silicone sheath instead of a conventional elastic bandage, to avoid the development of oedema and bottlenecks. The sheath is positioned for 1 h twice a day and progressively increased to 14 h a day. Once the stump is ready, usually from 7–10 days after surgery, a new system with silicone suspension cuff is applied, which differs from classic rigid cuffs for the flexible cup, allowing distal support. After delivery of the temporary prosthesis, 5–7 days after admission, it is possible to start prosthetic rehabilitation. After discharge from the unit, when the definitive prosthesis is available, the patient will again be admitted to the rehabilitation unit to start a new rehabilitation programme for at least 2 weeks, and thereafter the patient is followed in outpatient basis with the same medical and physiotherapy team to enable continuity of care. Even after patients have become independent in the management of their prosthesis and in activities of daily living, they are followed up every 2 months for 2 years, in order to address any new requirements or changes in their clinical status. Our previous experience has demonstrated considerable satisfaction among amputated patients, due to the advantages of early rehabilitation and use of a prosthesis. The same protocol was applied to patients amputated as a result of COVID-19. Future studies are needed to outline the correct rehabilitation programme for amputated COVID-19 patients.

Conclusion

Coagulation changes related to SARS-CoV-2 result from a series of thrombotic changes that complicate recovery from this devastating disease. The rehabilitation management of patients amputated due to COVID-19 ALI is based on a multidisciplinary approach to the clinical and functional needs of disability. Neuropsychological and nutritional support is important for early rehabilitation, enabling functional recovery and adequate stump management. A dedicated programme for this specific group of patients is advantageous to warrant the best functional outcome and QoL.

The authors have no conflicts of interest to declare.

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