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CASE REPORT

BENEFIT AND SAFETY OF INCOBOTULINUMTOXINA FOR EARLY MANAGEMENT OF POST-STROKE SPASTICITY IN A PATIENT WITH SARS-COV-2: A CASE REPORT

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Objective: **To describe a case of early management of post-stroke spasticity treated with incobotulinumtoxinA (IncoA) in a patient with SARS-CoV-2 (COVID-19). Scarce information is available on this subject, as the COVID-19 pandemic has necessitated postponement of interventions in infected and clinically suspicious patients.**
Case report: **A 58-year-old woman presenting with ischaemic stroke, was infected with SARS-CoV-2 virus due to nosocomial contact. Despite clinical improvement, the patient developed early spasticity. Modified Ashworth Scale (MAS) was grade II in her left elbow, wrist flexors and left gastrocnemius. IncoA was injected, using ultrasound guidance, in her upper and lower limbs. No complications were reported after the procedure. Two weeks afterwards, there was an improvement in her motor balance and spasticity, MAS was graded I in the left elbow, wrist flexors, and II in the left gastrocnemius. At 12 weeks, the patient reported improvement at a global level, with increasing independence and functionality.**
Conclusion: **This case indicates the benefits and safety of IncoA for early treatment of post-stroke spasticity in a patient with confirmed SARS-CoV-2. Despite the current status of national healthcare systems due to the COVID-19 pandemic, increased efforts should be made to avoid discontinuation of treatment for spasticity.**

Key words: incobotulinumtoxinA; botulinum toxin; stroke; spasticity; SARS-CoV-2.

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LAY ABSTRACT

One-third of patients with stroke develop spasticity, which induces stiffness, fibrosis, and atrophy. In early management of stroke it is important to minimize these consequences. However, the COVID-19 pandemic has resulted in the postponement of interventions in infected and clinically suspicious patients. We report here a case of a patient who was infected with SARS-CoV-2 virus while staying in hospital after a stroke and developed early spasticity. We report the patient's recovery, including treatment with incobotulinumtoxinA for spasticity. The relevance for clinical practice is that the early treatment of post-stroke spasticity with incobotulinumtoxinA was effective, with a favourable safety profile, in this patient with SARS-CoV-2 infection. Despite the current status of national healthcare systems due to the COVID-19 pandemic, greater efforts should be made to avoid the discontinuation of treatment for spasticity.

Post-stroke motor disorders present a variety of symptoms; such as spasticity, which results from impaired reflex function and induces stiffness, fibrosis and atrophy (1). Spasticity occurs in approximately 30% of stroke patients, within the first days or weeks of the event. It primarily affects the elbow (up to 79% of cases), wrist (66%) and ankle (66%) (1). Management of spasticity includes physical and occupational therapy, orthoses, pharmacological treatment, orthopaedic surgery, and neurosurgery. Intramuscular injections of botulinum toxin type A (BoNT-A) for spasticity have been shown to be effective, increasing the ability to mobilize both upper and lower limbs and improving the patients' autonomy (1, 2–5). BoNT-A inhibits the release of acetylcholine

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at the neuromuscular junction, which leads to a reduction in muscle contraction. To date, there are 3 different commercialized BoNT-A products. Of these, incobotulinumtoxinA (IncoA; Xeomin®, Merz Pharma España S.L., Madrid, Spain) is the only one that does not contain complexing proteins, and thus has reduced immunogenic potential (4). Furthermore, IncoA has proved effective in treating diverse musculoskeletal disorders characterized by muscle hyperactivity (6). The effectiveness of the combination of BoNT-A injections with an upper limb therapy programme is controversial. However, it might provide added value in some patients with subacute stroke, who are diagnosed with early spasticity (7).

The recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has necessitated reorganization of non-urgent clinical interventions, such as the treatment of long-term spasticity with BoNT-A (8). The prolonged suspension of activities has exposed patients to disability. Real-world evidence on the impact of the coronavirus disease-19 (COVID-19) pandemic on the management of patients with spasticity is scarce, and largely based on subjective surveys (9, 10). In addition, some of the surveys have excluded patients with confirmed SARS-CoV-2 infection or those who have developed related symptoms after the last injection (9). Similarly, research regarding the effectiveness and safety of BoNT-A injections with concomitant SARS-CoV-2 infection is very scarce (9).

We report here a case of administration of IncoA for early treatment of post-stroke spasticity in a patient with confirmed SARS-CoV-2.

CASE REPORT

A 58-year-old woman presented with right ischaemic stroke. On arrival at the emergency room, the stroke code was not activated because the time of evolution was longer than 48 h. Computed tomography (CT) angiography and cranial CT revealed a total anterior circulation infarction, with an atherothrombotic profile due to previous stent occlusion. Her clinical history included hypertension, dyslipidaemia, moderate ischaemic heart disease, with dyspnoea graded as II–III/IV according to the New York Heart Association classification, a lateral non-ST elevation myocardial infarction, and an episode of transient ischaemic attack in 2015. The cranial CT was repeated after 7 and 10 days, showing no significant changes, compared with the last control. At 14 days, cranial magnetic resonance (CMR) was performed, with similar findings to the initial CT. CMR revealed subacute ischaemic lesions in the territory of the right middle cerebral artery, suggestive of deep border infarcts secondary to ipsilateral carotid stenosis **(Fig. 1)**. The patient was hospitalized and followed-up for the study. She had left hemiplegia and intelligible dysarthria, scoring 10 on the National Institute of Health Stroke Score (NIHSS). The patient scored 4 in the modified Rankin Scale (mRS), and 35 points in the Barthel Index. During hospitalization, the patient received early intensive rehabilitation treatment.

After 4 days of treatment, a polymerase chain reaction (PCR) test for SARS-CoV-2 was positive, due to nosocomial contact.

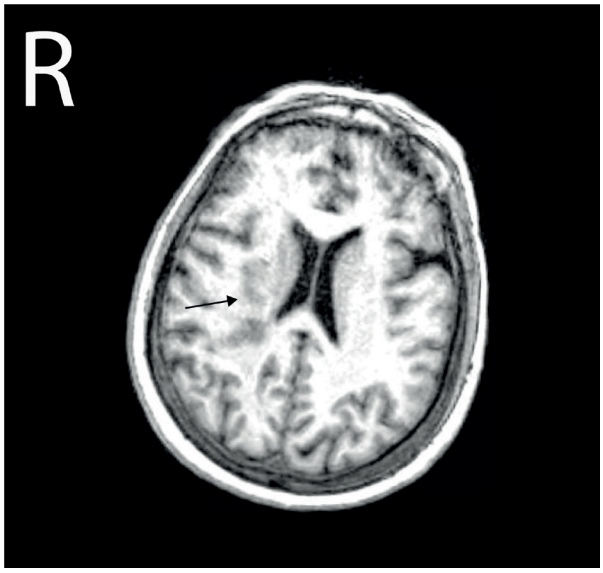

Fig. 1. Cranial magnetic resonance axial section in sequence Standardized T1 weighted 3D Turbo Field Echo (sT1W 3D TFE).

The patient developed asymptomatic SARS-CoV-2 infection, being haemodynamically stable, afebrile and without respiratory symptoms. She was subsequently moved to the COVID-19 area in the hospital, where the rehabilitative treatment was maintained.

Subsequent monitoring was carried out between the rehabilitation, neurology and internal medicine departments. Despite clinical improvement during hospitalization, the patient developed early post-stroke spasticity **(Fig. 2)**. Modified Ashworth Scale (MAS) was grade II in her left elbow and wrist flexors, and in the left gastrocnemius. The patient experienced pain on passive mobilization, scoring 8 points in the visual analogue scale (VAS) and 0.72 points in the European Quality of Life-5 Dimensions (EQ-5D)-5L questionnaire.

Fig. 2. Elbow and wrist flexors in paretic left upper limb in patient before being treated with incobotulinumtoxinA.

She was then injected with 330 units (U) IncoA (Xeomin®) under ultrasound guidance in the following muscles: biceps brachii (100 U, 2 sites 50 U); brachialis (50 U), flexor carpi radialis (40 U), flexor carpi ulnaris (40 U) and left gastrocnemius (100 U, 60 U medial plus 40 U lateral). The administration of IncoA was performed according to the standard indications, with adequate personal protective equipment (PPE) and aseptic protocols. PPE was used by the 2 doctors who injected IncoA, and operated the ultrasound equipment (screen, probe and probe cable). There were no complications after the procedure.

Two weeks later there was an improvement in strength and spasticity, MAS was graded I in the left elbow and wrist flexors, and II in the left gastrocnemius. VAS pain score was 3 points. After several positive PCR tests for SARS-CoV-2 infection and 20 days of isolation, a serology test detected immunoglobulin G (IgG) antibodies against SARS-CoV-2. Consequently, the patient was discharged from hospital and continued the rehabilitative treatment on an outpatient basis. At the time of hospital discharge, the NIHSS score was 4 points. After 4 weeks, the patient was re-evaluated in consultation. The MAS was graded I in the elbow flexors, 0 in the wrist flexors, and I+ in the left gastrocnemius. The VAS pain score was 4 points. Disability and functional measures included an mRS of 4 and Barthel Index of 45 points. The EQ-5D-5L questionnaire score was 0.924 points. At the 12-week follow-up visit, the patient reported improvement at a global level, together with increasing independence and functionality (Barthel Index 65 points). Furthermore, her motor balance was almost normal in the left hemi body, and spasticity remained stable at all levels. The MAS was graded I+ in the elbow flexors, and I+ in the gastrocnemius.

DISCUSSION

During the COVID-19 pandemic some non-urgent interventions have been suspended or postponed, including BoNT-A administration (8). Furthermore, when a patient has experienced fever or respiratory symptoms related to COVID-19, the clinical recommendation during the pandemic has been to not perform the procedure (8). In Italy, 151 patients were surveyed regarding the effects of discontinuing BoNT-A injections in the long-term for spasticity after stroke or traumatic brain injury (9). Participants were excluded if they had confirmed SARS-CoV-2 or similar symptoms after the last injection. A perceived worsening in spasticity was reported in most patients (72.2%), and 70.9% considered their quality of life was negatively affected. The majority of participants (77.4%) considered that BoNT-A should not be discontinued during the pandemic. In another survey performed in a German cohort, the effects of a 6-week discontinuation of BoNT-A was assessed in patients with diverse pathologies regarding long-term treatment (10). Of 9 patients diagnosed with spasticity, 37.8% considered that the shutdown of the centre had caused a reduction in their quality of life. Moreover, almost all patients experienced repeated muscle hyperactivity and muscle pain (depending on the disease). In this scenario, and to the best of our knowledge, this is the first report of a patient with confirmed SARS-CoV-2 who has been effectively treated with IncoA to palliate early post-stroke spasticity. It is notable that there were no complications after the injection of IncoA in the presence of the virus. SARS-CoV-2 infection did not alter the proven benefits and safety of IncoA for the early management of post-stroke spasticity.

There is extensive evidence for treatment with IncoA in both upper and lower limbs of spasticity caused by cerebral events. Santamato et al. performed a prospective, open-label study in 71 patients to evaluate the efficacy of treating lower limb spasticity after a cerebral event for at least 5 months, injecting IncoA in the soleus, medial and lateral gastrocnemius, with a maximum total dose of 180 U (2). Patients experienced a statistically significant reduction in muscle tone and spasm. Dorsi-flexion increased at 30 days and was maintained for 3 months. Kaňovský et al. conducted a *post hoc* analysis to evaluate the impact of repeated IncoA injections on muscle tone, disability, and caregiver burden in 465 adults with upper-limb spasticity after a stroke (5). Patients were injected with 400 U IncoA at 12-week intervals or ≤400 U at ≥12-week intervals (depending on clinical need) in the elbow, wrist, finger, thumb flexors and forearm pronator. Patients showed sustained improvements in all the items assessed. The MAS evidenced continuous improvement for 4 weeks after the injection (–3.23 vs –1.49 for the placebo group), and subsequent cycles. Santamato reviewed the efficacy of the treatment of spasticity, and stated that several studies and meta-analyses positioned BoNT-A treatment as the first choice for the recovery of focal spasticity (3). He concluded that this therapeutic approach was able to reduce functional disability and improve quality of life. There is no agreement regarding the prevalence of spasticity onset after a cerebral event, which is related to difficulty in identifying its early development, discerning between spastic-dystonia, stiffness or contractures, etc. (3). Nevertheless, there is increasing interest in the use of botulinum toxin A during the early phase of stroke, in order to minimize the consequent stiffness and contractures (3). In concordance with the literature, the injection of IncoA in the current case resulted in improvement in early spasticity of the upper and lower limbs. Initially, MAS was graded II in the left elbow and wrist flexors, as well as in the left gastrocnemius. Two weeks after treatment, MAS grade was I in the left elbow and wrist flexors, and II in the left gastrocnemius. Furthermore, this was associated with a reduction in pain (VAS pain score from 8 to 3) and in improvement in quality of life measured by the (EQ-5D)-5L questionnaire (from 0.72 to 0.924 points). The improvement was also sustained for up to 12 weeks (final follow-up visit).

IncoA has also demonstrated a favourable safety profile. Wissel et al. assessed the efficacy and safety of doses of IncoA up to 800 U in patients with spasticity due to cerebral causes (4). Dose escalation did not affect the tolerability or safety, and no serious treatment-related adverse events were observed. None of the patients developed neutralizing antibodies. This adequate safety profile could be due to

the more purified form of IncoA. This BoNT-A product does not include complex-forming proteins, which are associated with potential immunogenicity (4). The current case report is in agreement with the literature, since no complications were encountered after the intervention.

In conclusion, the current case indicates the benefit and safety of IncoA for early treatment of post-stroke spasticity in a patient with confirmed SARS-CoV-2. Despite the current status of national healthcare systems due to the COVID-19 pandemic, greater efforts should be made to avoid discontinuation of treatment for spasticity.

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Conflicts of interest. Carlos Cordero-García has participated in training sessions as a trainer and as a speaker for the following companies: Merz Pharma, Allergan, IPSEN. María del Mar Sáenz de Tejada Sánchez has no conflicts of interest to declare.

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