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Case Report

Botulinum toxin type A treatment for persistent neuropathic pain in the soles after cervical spinal cord injury: A case report

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ABSTRACT

Subcutaneous botulinum toxin type A is recommended for neuropathic pain at the level of spinal cord injury. Herein, we present a 42-year-old female patient who presented to our outpatient clinic with neuropathic pain in the soles for eight years due to cervical long-segment myelitis. The patient had previously received various ineffective oral medications for the symptoms. Botulinum toxin type A was injected subcutaneously into bilateral soles. The patient was evaluated in the first, second, third, fourth, and sixth months after the injection. The daytime and nighttime Visual Analog Scale, Neuropathic Pain Questionnaire, Short Form-36, and Beck Depression Inventory scores improved during follow-up.

Keywords: Botulinum toxin, neuropathic pain, pain management, spinal cord injury, treatment.

Neuropathic pain is a common complication of spinal cord injury (SCI) that occurs in 53% of patients and severely affects quality of life.[1] Neuropathic pain usually presents within six months of SCI, is refractory to treatment, and persists for years.[2] Post-SCI neuropathic pain can be categorized into pain at and below the level of the SCI. The mechanisms underlying pain differ between these categories, thus requiring different treatment modalities.[3,4] Local pharmacological agents are recommended for pain at the level of the injury, potentially involving peripheral mechanisms. Treatment of post-SCI neuropathic pain is challenging and involves a trial-and-error process.[4]

Subcutaneous botulinum toxin type-A (BTX-A) is a local agent used to treat post-SCI neuropathic pain. Current guidelines recommend BTX-A as a second-line treatment for pain at, but not below, the level of the injury.[4] Botulinum toxin type-A has a short-term positive effect on neuropathic pain in patients with SCI; however, there is no evidence of long-term beneficial effects on quality of life and pain.[5,6] Herein, we describe a patient with cervical SCI who had neuropathic pain in the soles that was resistant to oral medication but found long-term relief through subcutaneous injections of botulinum toxin.

CASE REPORT

A 42-year-old female presented to our outpatient clinic with a burning sensation in the soles for eight years. The initial complaint began with pain and weakness in the shoulders, followed by rapid loss of strength in the upper and lower extremities within a few days and subsequent development of respiratory depression. The patient was diagnosed with long-segment myelitis extending from C2 to T1 with mass effect. The patient was treated in the intensive care unit for four months. During hospitalization, the patient entered cardiac arrest. A pacemaker was implanted, and tracheostomy was performed for prolonged intubation. Laboratory investigations of aquaporin-4

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and myelin oligodendrocyte glycoprotein antibodies and vasculitis markers were negative. The patient was treated with intravenous methylprednisolone and plasma exchange therapy. A written informed consent was obtained from the patient.

In the outpatient clinic, a neurological examination was performed according to the neurological classification of SCI developed by the American Spinal Injury Association (ASIA). The ASIA impairment scale (AIS) grade was C5 AIS D. According to the modified Ashworth scale, Grade 1 spasticity was present in the bilateral ankle plantar flexors. The patient was receiving pregabalin 600 mg/day for approximately five weeks and duloxetine 60 mg/day for approximately 10 weeks for the neuropathic symptoms. Pregabalin and duloxetine were first prescribed to the patient 14 and eight months ago, respectively. The patient had previously received various medications that were ineffective, including amitriptyline, gabapentin, tramadol, and nonsteroidal anti-inflammatory drugs. The underlying peripheral neuropathy was unremarkable. The patient experienced pain in the soles, which increased spontaneously and was aggravated by walking. The pain was constant throughout the day and night, manifesting as burning, stabbing, or tingling. The Douleur Neuropathique 4 and Leeds Assessment of Neuropathic Symptoms and Signs scores were 6 and 21, respectively. Contrast-enhanced magnetic resonance imaging of the cranium and cervical and thoracic spines was performed due to the patient's increasing pain in the soles. No changes were observed in the magnetic resonance images. Botulinum toxin type A was subcutaneously injected into the bilateral soles. After sterilization using ethyl alcohol, 25 injection sites were marked using a sterile pen (Figure 1). Botulinum toxin type A (200 IU)[5] was diluted in 5 mL of saline to ensure an equal amount was injected into each marked site (0.1 mL [4 IU] of the mixture per site) using a 26-gauge needle. No side effects were observed after the injection. The patient was followed up for six months. The pregabalin and duloxetine doses the patient received during the six-month follow-up after injection were the same as the preinjection doses. The daytime and nighttime Visual Analog Scale for pain, Neuropathic Pain Questionnaire, Short Form-36, and Beck Depression Inventory scores improved during follow-up. However, the sleep quality, assessed by the Pittsburgh Sleep Quality Index, remained unchanged (Table 1).

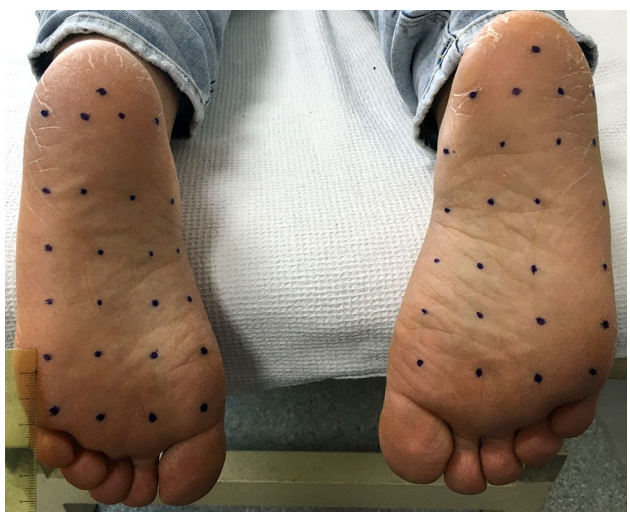

Figure 1. Botulinum toxin type A injection sites.

DISCUSSION

Although BTX-A has been used to treat various types of neuropathic pain for years, its mechanism of action is unknown. One possibility is that it reduces peripheral nervous system sensitization by inhibiting the release of certain peripheral neuropeptides or by retrograde transport from the peripheral nerve terminals to the spinal cord.[6] Although the first report of using BTX-A to treat post-SCI neuropathic pain was published in 2003,[6,7] data on the potential benefits of this treatment are limited.

In a study by Han et al.,[5] patients with post-SCI neuropathic pain were treated with BTX-A or saline injections. Botulinum toxin type A (200 IU) was injected in a checkerboard pattern over the area with the most pain. Each patient received 40 injections with a minimum distance of 1 cm between injection sites. The investigators found that pain was reduced at four and eight weeks after BTX-A administration; however, the treatment did not improve quality of life. The findings suggest that BTX-A treatment may be effective in patients with post-SCI neuropathic pain below the level of the injury. However, because the patients were only followed up for eight weeks, the long-term effects and risks of the treatment were not assessed. We followed our patient for six months and found that well-being, quality of life, depression, and pain scores improved during the six-month follow-up. Han et al.[5] did not report the specific BTX-A injection sites. It may be that the long-term improvement in the well-being of our patient was related to the injection of BTX-A into the soles of the feet.

TABLE 1
Pre- and postinjection evaluation scores

	Before injection	After injection 1st month	After injection 2nd month	After injection 3rd month	After injection 4th month	After injection 6th month
VAS daytime	10	2	5	5	5	5
VAS nighttime	10	2	5	4	5	5
Neuropathic Pain Questionnaire	1.122	-0.078	0.032	0.132	0.112	0.128
PSQI						
Subjective sleep quality	2	1	2	1	1	1
Sleep latency	0	0	0	0	0	0
Sleep duration	0	0	0	0	0	0
Sleep efficiency	0	0	0	0	0	0
Sleep disturbance	1	1	2	2	1	2
Use of sleep medication	0	0	0	0	0	0
Daytime dysfunction	2	2	2	2	2	2
Global score	5	4	6	5	4	5
Short Form-36						
Physical function	20	55	60	55	60	55
Role limitations due to physical health	0	0	0	0	0	0
Role limitations due to emotional problems	0	33.3	33.3	33.3	33.3	33.3
Energy/fatigue	0	40	40	30	40	40
Emotional well-being	0	36	12	28	30	36
Social functioning	0	62.5	12.5	37.5	40.5	37.5
Pain	0	67.5	50	45	40	45
General health	5	10	0	5	10	10
Health change	25	75	0	25	0	0
Beck Depression Inventory	25	13	16	19	16	16

VAS: Visual Analog Scale; PSQI: Pittsburgh Sleep Quality Index.

In another study, patients with post-SCI neuropathic pain at the level of injury received BTX-A (400 IU) injections into the area of worst pain (80 in total).[8] Since the investigators were unable to meet the target sample size, the findings were presented as a case series. Although the results were not statistically significant, most of the participants in the BTX-A group experienced some degree of pain relief by two to four weeks after treatment compared to the placebo group. In some patients, pain relief continued up to 12 weeks. While some patients reported improvements in day-to-day activities, mood, sleep, and quality of life, the duration varied, and only a single question was used to assess improvement. Moreover, the investigators did not conduct a comprehensive inventory, such as the Short Form-36 or Pittsburgh Sleep Quality Index, as performed in our patient.

The beneficial effects of BTX-A persisted for six months in our patient. No reports of pain relief for six months exist in patients with post-SCI neuropathic pain, although one study found that BTX-A treatment reduced pain for six months in patients with non-SCI-associated neuropathic pain.[5] The mechanism underlying the long duration of action of BTX-A is unknown;[5] however, De la Torre Canales et al.[9] suggested that the long-term effect is associated with modulation of the opioidergic and GABAergic systems.

Several limitations of this report should be acknowledged. The maximum dose of BTX-A used to treat neuropathic pain varies widely in the literature, making it challenging to standardize the optimal dose for achieving the best effect.[6] Another consideration is that the intensity of pain can be influenced by various daily factors, such as the individual's mood and exposure to stress.[4] During the six-month follow-up period in which the effectiveness was assessed in our patient, active monitoring of all factors that could affect the process could not be conducted. However, as no other factors reported by the patient were identified, the observed positive effect was attributed to BTX-A. Lastly, the presence of accompanying polyneuropathy in our patient was ruled out through electromyography; however, the exclusion of small fiber neuropathy could not be definitively confirmed through electrophysiological methods,

leaving uncertainty about whether this condition is concomitant.

In conclusion, the most important finding of this case study is that quality of life, depression, and neuropathic pain scores improved during six months of follow-up after local injection of BTX-A in a patient with neuropathic pain below the level of the SCI. Subcutaneous BTX-A injections may reduce pain and improve quality of life in patients with neuropathic pain that is resistant to oral medication and below the level of the injury. Botulinum toxin type A has no systemic side effects at current doses, and it is nonaddictive and minimally invasive.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept: A.M., B.G.T.; Control/supervision, materials: A.M., U.U.; Data collection, analysis, literature review, writing the article, critical review: A.M., B.G.T., U.U.

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