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Botulinum toxin treatment for intractable allodynia in a patient with complex regional pain syndrome: A case report

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Abstract

The right hand of a 58-year-old female was compressed by a compression machine and subsequently began to show pain. She was diagnosed with complex regional pain syndrome type 2 according to the Budapest criteria. Conventional therapy was ineffective for her allodynia. After subcutaneous injection of botulinum toxin, the subject's allodynia substantially improved. Subcutaneous injection of botulinum toxin could effectively treat patients with complex regional pain syndrome and intractable allodynia. Clinical studies with larger sample sizes are needed to evaluate the efficacy of and selection of patients for botulinum toxin treatment of complex regional pain syndrome.

Keywords: Complex regional pain syndrome, botulinum toxin, pain, allodynia

INTRODUCTION

Complex regional pain syndrome (CRPS) is a distressing pain disorder that presents as disparate changes in sensory, vasomotor, or motor systems, as well as edema.[1] Few cases of CRPS resolve within 12 months of onset, while most patients suffer from unremitting pain and devastating disability.[2] Despite varied pain control management strategies, there is no cure and outcomes remain less optimistic.

Botulinum toxin (BTX) treatment has been previously been attempted for pain relief in CRPS.[3] Independent of muscle relaxation, BTX is known to have an antinociceptive effect.[4] BTX is the suggested third-line drug for neuropathic pain, a main feature of CRPS.[5] Peripheral sensitization by neurogenic inflammation and central sensitization contribute to CRPS.[6] BTX reduces neurogenic inflammation by suppressing nociceptive neuropeptides and also has the potential to inhibit central sensitization.[7] BTX injections have also been used for pain relief in central and peripheral neuropathic pain conditions.[8,9]

The analgesic effects of BTX in CRPS have shown heterogenous results. Some authors have reported substantial pain relief, while others have argued that the procedure was too painful to tolerate and had no effect.[10,11] Such diverse outcomes of BTX treatment might be due to the complex pathogenesis and heterogenous clinical spectrums associated with CRPS. Hyperalgesia and allodynia are key clinical features of CRPS.[12] This report describes a patient for whom BTX treatment was effective in relieving severe allodynia associated with CRPS.

CASE REPORT

A 58-year-old female was referred for the management of CRPS affecting her right hand. Four weeks prior, she suffered a crush injury on the hand at work. Upon physical examination, her hand showed severe allodynia, altered skin-color, edema, and motor changes such as tremor and weakness. A thermographic test showed a right hand temperature that was higher by 2.6°C. A three-phase bone scan showed increased trace uptake at all blood flow, pool, and delayed images in the right wrist and hand, which is indicative of CRPS.[13] Electrodiagnostic studies revealed right median and ulnar neuropathy at the wrist. The patient was then diagnosed with CRPS type 2, according to the Budapest criteria.[1]

She was admitted for intensive management composing of rehabilitation and pain interventions. She was prescribed oral pulse corticosteroids at an initial dose of 40 mg (body weight 48 kg). Although the swelling of the hand improved after oral steroid therapy, the mechanical allodynia remained. Conventional pain procedures

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encompassing peripheral nerve blocks (6 times for median and ulnar nerves), stellate ganglion block (twice) and cervical epidural steroid injection (6 times) were performed for 2 months but failed, providing only slight pain relief for several hours. Epidural catheter insertion for pain control was also attempted, but the catheter was withdrawn due to the insertion site pain (Table 1). Adrenal insufficiency, which may have been iatrogenic due to steroid treatment, was subsequently detected.

As described above, interventions were ineffective and steroid was no longer available. The patient's allodynia and neuropathic pain continued to be excruciating, making all activities of daily life using her right hand impossible. Subcutaneous (SC) injection of BTX into her right hand was then attempted. BTX injection was performed using botulinum toxin A (Meditoxin®, MedyTox Inc., Korea). Because the palm is a pain-sensitive area, regional anesthesia was performed by blocking the median and ulnar nerves at the forearm level (Figure 1B and 1C). BTX was subcutaneously injected into the right palm at a total dose of 50 IU across 20 sites. Injections were performed under ultrasound guidance to prevent intramuscular injection (Figure 1A and D). The allodynia of her right hand significantly improved the first day after BTX injection. She regained the use of her right hand for eating and dressing as the pain subsided. The pain relief was sustained for 3 weeks. A second round of BTX injections at the same sites with an increased dosage of 100 IU was then performed. The pain also improved significantly after the second set of injections (Figure 1E). The pain reduction lasted over 4 weeks and the patient was discharged successfully. The pain relief of 2nd BTX was about 8 weeks and 3rd BTX was done at 27 weeks from the first visit. There was no change in the pain medications (pregabalin 25 mg bid, meloxicam 7.5 mg bid). The severe allodynia was diminished substantially from the next day after the 3rd BTX injection. At recent follow up about 58 weeks after onset of symptom, the patient's neuropathic pain and allodynia in the right hand and palm became as severe as before BTX injection. The efficacy of 3rd BTX seemed to be longer than the previous two injections, about 31 weeks (3 (1st and 2nd BTX) → 8 (2nd and 3rd BTX) → 31 weeks (after 3rd BTX)).

DISCUSSION

Although treating CRPS is challenging, early intervention is recommended to prevent the transition to the chronic phase, when serious problems and sociomedical burdens can arise.[2,14]

Previous studies using BTX as a treatment option for CRPS showed heterogenous results. In one case report, BTX was injected subcutaneously into the dorsum of the left hand in a patient with CRPS type 1 and provided pain relief.[10] By contrast, intradermal injection of BTX in patients with severe allodynia was poorly tolerated and had no effect on pain.[11] Previous studies summarized in Table 2. BTX is thought to block pain mediators, reduce neurogenic inflammation, deactivate sodium channels within the peripheral nervous system, and travel to the central nervous system (CNS) via axonal transport.[15] In the patient in this case, the analgesic effect appeared on the first day after BTX injection, suggesting that

Table 1: Conventional treatment options before BTX injection

Duration	Conventional treatment (number of attempts)				
	Steroid pulse therapy	**Peripheral nerve block**	**Cervical epidural block**	**Stellate ganglion block**	**Epidural catheter insertion**
Week 0-4	1				
Week 5		2			
Week 6			2		1
Week 7				2	
Week 8-11	1	1	1		
Week 12		1	1		
Week 13		1	1		
Week 14		1	1		
Total	2	6	6	2	1

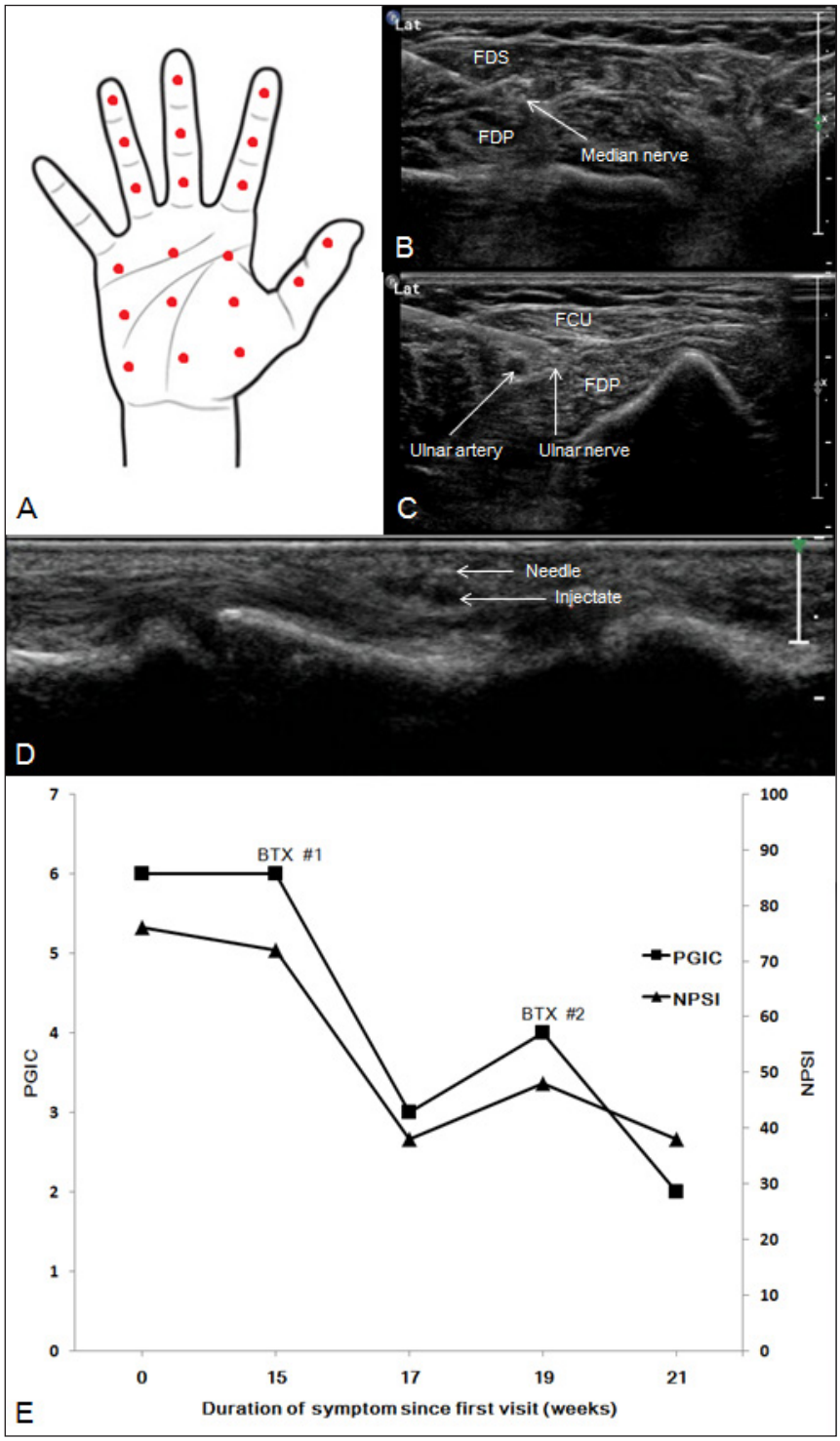

Figure 1. Multiple subcutaneous BTX injection procedure.
(A) Diagram of injection sites on the patient's hand. (B, C) Ultrasound-guided median (B) and ulnar (C) nerve block for regional anesthesia prior to subcutaneous BTX injection. (D) Ultrasound-guided subcutaneous BTX injection. (E) Pain scores of the patient before and after the procedure.
Abbreviation: FDS: flexor digitorum superficialis; FDP: flexor digitorum profundus; FCU: flexor carpi ulnaris; PGIC: patient global impression of change; NPSI: neuropathic pain symptom inventory; BTX: botulinum toxin

Table 2: Literature review table on the use of botulinum toxin in complex regional pain syndrome

Study Design	Number of participants	Dose	Injection method	Results	Reference
Before-after study (1999)	11 participants	25–50 U per site (up to 300 U)	Intramuscular Muscle selected based on the patient's report of maximal pain	Improved VAS, allodynia, hyperalgesia, and skin color after 6 to 12 weeks	Argoff *et al*.[17]
Case study (2005)	2 participants	60 U and 75 U BTX for each	Intramuscular Intrinsic finger flexors and wrist muscles	Improvement in dystonia and pain for up to 8 months	Lauretti *et al*.[18]
Randomized, double-blind, placebo-controlled crossover (2009)	9 participants	75 U BTX + 0.5% Bupivacaine 10 ml vs. 0.5% Bupivacaine 10 ml	Lumbar sympathetic block by fluoroscopic guidance	Analgesic duration: 71 days with BTX compared with fewer than 10 days without BTX	Caroll *et al*.[19]
Case study (2010)	2 participants	20 U per site (200 U and 240 U for each)	Intramuscular Trigger points of affected muscles	Decreased pain for 3 years in the first patient	Safarpour *et al*.[20]
Randomized, double-blind, placebo-controlled (2010)	14 participants (8 BTX group, 6 normal saline group)	5 U per site (40–200 U)	Intradermal and subcutaneous injection into the allodynic area	No improvement in pain scores probably due to poor injection tolerance in more advanced CRPS	Safarpour *et al*.[11]
Retrospective chart review (2011)	37 participants	10–20 U per muscle (100 U)	Intramuscular electromyography guided BTX injections	Significant reduced pain at 1 month and average pain reduction by 43%	Kharkar *et al*.[3]
Case study (2012)	1 participant	5 U per site (100 U)	Subcutaneous BTX injection on the dorsum of left hand	Improved pain intensity for 3 months	Birthi *et al*.[10]
Case study (2015)	2 participants	5,000 U BTX B + 0.25% Levobupiva-caine 5 ml	Lumbar sympathetic block by fluoroscopic guidance	Improved VAS, allodynia, coldness and skin color after 2 months	Choi *et al*.[21]
Before-after study (2018)	20 participants	10 U per site (up to 100 U) Repeated each month	Subcutaneous injection at each grid of 1 by 1 cm on the hypersensitive area after nerve block with 1% lidocaine	Average pain reduction by 2.05 on VAS scale Maximum pain reduction by 9 sessions	Lessard *et al*.[22]
Case study (2019)	1 participant	BTX 100 U	Intra-articular gleno-humeral joint injection	Pain relief for 4 months	Bellon *et al*.[23]

VAS: visual analogue scale; BTX: botulinum toxin; BTX B: botulinum toxin B

BTX was acting on SC nociceptive fibers rather than entering and acting on the CNS via axonal transportation.

It is known that the antispasticity effect of BTX is effective for about 3 to 4 months but antinociceptive activity is shorter than 3 to 4 months. And duration of BTX is related to dose.[16] In this case, the duration of the effect was about 3-4 weeks. When the dose was increased from 50 IU to 100 IU, the duration of action increased from 3 weeks to 4 weeks, so the dose may have been insufficient to have adequate effect on the patient.

The procedure in this case report was slightly different compared to procedures in previous studies. It was not only well tolerated by the patient, but also effective for pain control. First, this procedure included median and ulnar nerve block prior to the SC injection, to allow for tolerance of the BTX injections. Second, ultrasound guidance was used for SC injection of BTX to prevent intramuscular injection from occurring. Finally, BTX was injected into the palm, not the dorsum.

SC injection of BTX could be an effective intervention in patients with CRPS and intractable allodynia. Clinical studies with larger sample sizes are needed to evaluate the efficacy of and selection of patients for BTX treatment of CRPS.

DISCLOSURE

Conflict of interest: None

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