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Subcutaneous Botulinum Toxin Type-A Injections for the Treatment of Central Neuropathic Pain in a Patient With Multiple Sclerosis – A Case Report

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Background: Neuropathic pain is a common, but difficult-to-treat, condition affecting the quality of life of many. It is prevalent in patients with multiple sclerosis (MS), an autoimmune chronic inflammatory disease of the central nervous system. Treatments, such as gabapentin, pregabalin, tricyclic antidepressants, serotonin, and norepinephrine reuptake inhibitors, are insufficient. As a result, botulinum neurotoxin type A (BoNT-A) has been explored for its effects on pain control with neuropathic pain.

Case Report: We present a 59-year-old woman with chronic neuropathic pain and MS. She presented to us with allodynia in the lateral portion of her left trunk, radiating into her breast to the nipple. The patient reported improvement in pain after subcutaneous injections of BoNT-A over the area of pain.

Conclusions: In the present case report, we highlight the effectiveness of subcutaneous BoNT-A for the treatment of refractory central neuropathic pain in MS.

Key words: Botulinum toxin type-A, central neuropathic pain, multiple sclerosis, subcutaneous injections, at-level pain

BACKGROUND

Neuropathic pain is a common and difficult-to-treat condition that affects the quality of life of many patients. Its definition has undergone several iterations, with the most recent definition, set forward by the International Association for the Study of Pain, which defines it as: "pain caused by a lesion or disease of the somatosensory nervous system" (1-3). This definition allows for improved representation of the clinical description to include a broad category of disease states and syndromes. The incidence of neuropathic pain is profound, with some recent data estimating 7% to 10% of the general population and 20% to 25% of patients with chronic pain are suffering from its effects (3-6).

Currently, the guidelines for treatment of neuropathic pain recommend the use of medications, such as gabapentin, pregabalin, serotonin, norepinephrine reuptake inhibitors, and tricyclic antidepressants, as first-line treatments (7). Unfortunately, even with these medications, it is estimated that fewer than 60% of patients sustain a meaningful improvement in neuropathic pain (8). Because of the lack of treatment options for a sizeable portion of patients, many second-line options have been investigated as possible treatment modalities. Of

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these options, botulinum neurotoxin type A (BoNT-A) injections have been investigated for the treatment of refractory neuropathic pain (9).

BoNT-A is commonly used in the treatment of spasticity and dystonia due to its profound effect on hyperactive muscles. Recently, more research has focused on its effect on analgesia, separate from its effect on muscle activity (10). Typically, BoNT-A is injected intramuscularly for the treatment of spasticity and dystonia. Recently, subcutaneous BoNT-A has been considered as a treatment option for patients with refractory neuropathic pain (11-14). One study (15) documented a decrease in noxious mechanical pain sensitivity in healthy volunteers undergoing intradermal BoNT-A injections. While its effects on the presynaptic binding of soluble N-ethylmaleimide-sensitive factor activating protein receptor proteins are well understood and accepted, its effects on analgesia are still unclear (16).

In multiple sclerosis (MS), a chronic autoimmune inflammatory disease of the central nervous system, it is estimated that at least 26% of patients suffer from neuropathic pain (17,18). This MS-associated neuropathic pain is commonly referred to as central neuropathic pain (CNP), which develops secondary to demyelination and plaque formation in the brain and spinal cord (18-20). Previously, BoNT-A has been used in MS for the treatment of spasticity, urinary symptoms, trigeminal neuralgia, postherpetic neuralgia, migraine, and tremors (9, 21-26). While previous studies have used BoNT-A to address other causes of pain in patients with MS, to our knowledge, the use for the treatment of CNP has not been documented (27,28).

Our report aims to describe the successful treatment of CNP that coincides with the level of a demyelinating lesion documented on magnetic resonance imaging (MRI). This case report aims to add to the small but growing body of evidence supporting the use of BoNT-A for neuropathic pain, especially those with central pain contribution.

CASE PRESENTATION

Our case describes a 59-year-old female veteran with a history of MS and osteoporosis with multiple fractures, who presented with chronic neuropathic pain. Informed consent to write this case report was obtained from the patient. Over the year prior to her evaluation in 2023, she experienced allodynia in the lateral portion of her left trunk, radiating into her breast to the nipple. MRI, in 2021 and 2023, showed evidence of a "single demyelinating plaque involving the left hemicord at the T5 level." There was no spinal cord signal abnormality elsewhere (Fig. 1).

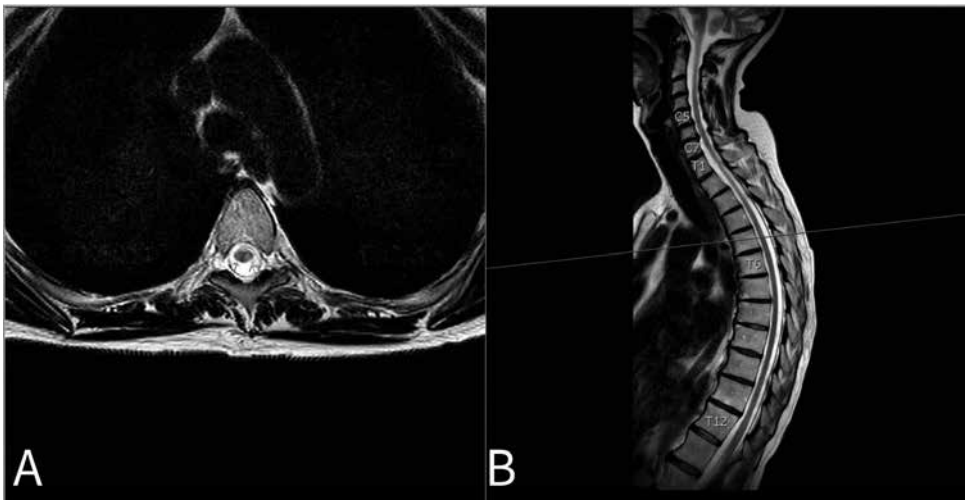

Fig. 1. MRI of thoracic spine in patient with MS. Imaging at the T5 level demonstrates a single demyelinating plaque involving the left hemicord.
A) Demonstrates an axial view at the T5 level of this patient's thoracic MRI. The 2 arrows indicate the single demyelinating plaque of the left hemicord. B) Demonstrates a sagittal view of the thoracic MRI with a line indicating the level at which the axial image was obtained. MRI, magnetic resonance imaging; MS, multiple sclerosis.

Treatment Technique

She was initially treated with gabapentin 900 mg 3 times a day and nortriptyline 50 mg nightly. She also tried lidocaine and capsaicin without improvement. Gabapentin was slowly titrated to 1,200 mg 3 times daily. Unfortunately, she had minimal success with these changes. At this time, the patient reported her pain to be a 9 out of 10 on a scale where 1 indicated no pain, and 10 indicated the worst pain she had experienced. The patient was offered a T5 transforaminal epidural steroid injection by interventional spine specialists, but she declined due to her osteoporosis and concern for steroid-related complications. Additionally, ultrasound-guided intercostal nerve blocks using 8 mL of 0.2% ropivacaine distributed over the second, third, and fourth ribs were trialed. She reported mild improvement in nerve pain at the conclusion of the procedure that only lasted for 2-3 hours. Other treatment options, such as diagnostic transforaminal epidural injection, could have been attempted to consider interventions, such as dorsal root ganglion radiofrequency ablation; however, these treatments are not being performed at our institution and so we discussed referral to the community should our interventions fail to provide relief. Other treatment options could also include interventions, such as intercostal peripheral nerve stimulation and spinal cord stimulation.

Given the lack of pain relief with previous interventions, the patient was consented for a subcutaneous BoNT-A injection for the treatment of refractory neuropathic pain. The patient again stated her preprocedure pain was a 9 out of 10. In the preprocedure exam, a focus on banding hypersensitive pain was identified in the lateral side of the breast at the level of the nipple, spreading laterally to the midaxillary line overlying the serratus anterior. In a similar method, as previously described by Chun et al (28), a grid measuring 10 cm wide x 5 cm tall was marked by creating 8 columns and 5 rows of injection targets, with the medial 3 columns spaced ~1 cm apart and the lateral 5 columns (Fig. 2) distributed evenly across the remaining grid width. Two hundred units of incobotulinumtoxinA were dissolved in 8 mL of preservative-free normal saline. The target areas were cleaned with Chloraprep™. Using a 30G 5/8" needle, 0.2 mL (5 units of incobotulinumtoxinA) was injected subcutaneously at each point for a total of 40 points. Each target was aspirated to minimize risk of intravascular uptake.

The patient experienced mild pain with injections but overall tolerated the procedure well. There was no blood loss. On postprocedure follow-up, the patient reported significant improvement in pain relief reporting a 6 out of 10 pain score. The patient eagerly scheduled a repeat procedure with the request to add additional columns laterally toward the midaxillary line. Three months later, the procedure was performed in the same manner, with the following exceptions: 1) A grid measuring 13 cm wide x 5 cm tall was marked by creating 10 columns and 5 rows of injection targets, with the medial 7 columns spaced ~1 cm apart and the lateral 3 columns spaced ~2 cm across the remaining grid width. 2) The lateral-most column was 17 cm lateral from the nipple. 3) Three hundred units of incobotulinumtoxinA were dissolved in 10 mL of preservative-free normal saline. 4) The target areas were cleaned with Chloraprep™. 5) Using a 30G 5/8" needle, 0.2 mL (6 units of incobotulinumtoxinA) was injected subcutaneously at each point for a total of 50 points. 6) Each target was aspirated to minimize the risk of intravascular uptake. Prior to the procedure, the patient again reported a 9 out of 10 pain. Following the procedure, the patient reported even more effective pain relief with a 5 out of 10 on the pain scale. There were no adverse effects reported in either procedure.

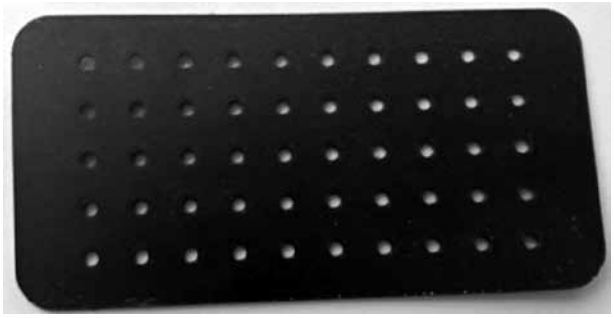

Fig. 2. Microcarbon fiber-filled nylon that was 3D printed into a flexible grid measuring 10 cm wide x 5 cm tall was marked by creating 8 columns and 5 rows of injection targets. This grid was used to mark injection targets as indicated in the body of the paper. 3D, 3-dimensional.

DISCUSSION

BoNT-A for Refractory Neuropathic Pain

Here, we describe the successful subcutaneous use of BoNT-A for the treatment of refractory neuropathic pain from a demyelinating lesion in a veteran with MS. While there is growing data on the use of this treatment for

refractory pain, to our knowledge, this is the first case of using subcutaneous BoNT-A to treat refractory CNP in a patient with MS. Furthermore, this study continues to demonstrate the effectiveness of a systematic grid application at the site of pain for BoNT-A injections. There are many patients suffering from neuropathic pain that are unable to achieve relief with current first-line treatments. In this case, our patient had substantial success with just one application of BoNT-A and elected to have the procedure repeated. By the time of our second injection, the patient reported slightly increased pain when compared to her prior postprocedural levels, and thus we opted for a higher dose of BoNT-A, this however remained within the previously established levels (27). BoNT-A could represent a promising therapeutic tool for the treatment of neuropathic pain as it continues to demonstrate efficacy and tolerability in multiple conditions (29). The development of new and effective treatments for neuropathic pain is paramount, as there is a strikingly high proportion of patients who are nonresponders to first-line therapies. In addition, there are several documented adverse effects of these medications, and a larger proportion of patients elect to discontinue treatment (7,30,31).

Safety Considerations

There are no current documented serious adverse effects of subcutaneous BoNT-A with only mild-to-moderate effects, including weakness, pain at injection sites, local skin reactions, flu symptoms, nausea, and vomiting, having been reported (29). Though not reported in literature on subcutaneous BoNT-A use, the risk of diffusion should be considered (32). Diffusion of BoNT-A beyond the intended area is of concern due to the possibility of local and systemic effects (32). As a result, patients could experience muscle weakness, though this has been more typically seen in intramuscular injections (33,34). There is also the botulinum toxin spreading to the systemic circulation, at which point it could lead to respiratory failure and death (34)

BoNT-A and Proposed Pain-Relief Mechanisms

Studies have shown that BoNT-A can inhibit the release of neuropeptides that facilitate nociception. Peptides include substance P, calcitonin gene-related peptide (CGRP), and glutamate (35). BoNT-A is known to inhibit the release of substance P from rat dorsal root ganglia neurons (36). An in vivo study (37) in rats demonstrated that BoNT-A can inhibit activity of C fibers, i.e., unmyelinated nerve fibers, that convey pain in trigeminal ganglia neurons. BoNT-A has also been documented to decrease the concentration of CGRP, an inflammatory neuropeptide that is associated with pain (38).

It has been suggested that the pain-relief effects of BoNT-A are driven by axonal transport from peripheral nerves to the central nervous system (39). Unilateral injections of BoNT-A have been shown to reduce bilateral acid-induced pain and bilateral paclitaxel-induced neuropathy in animal models (40). Radioactive iodine-labeled BoNT-A injected into a feline gastrocnemius muscle showed radioactivity in the sciatic nerve, then spinal ventral roots, and ipsilateral spinal cord by 48 hours. They also showed a small amount of radioactivity in the contralateral ventral roots (41). Previous studies have investigated subcutaneous injections of BoNT-A for the treatment of at-level neuropathic pain in spinal cord injury (SCI). Han et al (27) found a significant improvement in pain questionnaire scores and quality-of-life assessments in a double-blind, placebo-control trial testing 200 units of subcutaneous BoNT-A. Similarly, a study (28) on 8 patients with at-level pain from SCI demonstrated the effectiveness of this treatment. While this population differs slightly from our case, it further supports the use of BoNT-A at the site of pain for the treatment of CNP experienced in these populations.

Limitations

Our study has a few limitations. While the patient's symptoms were consistent, and she had imaging evidence that correlated with the described pain pattern, objective data with a standardized outcome measure would be more convincing for future studies. Lastly, our subcutaneous injections were performed palpation guided. Future studies could use ultrasound or electromyography (in which the absence of electrical activity would support subcutaneous placement) to confirm subcutaneous injection.

CONCLUSIONS

There is a need for alternative treatments for neuropathic pain. Given poor outcomes with first-line agents, clinicians have focused their attention on interventions, such as subcutaneous BoNT-A, for the treatment of refractory neuropathic pain. Our case report demonstrates a successful treatment of refractory neuropathic pain using a grid-based approach for subcutaneous BoNT-A injection. This study is the first to demonstrate this indi-

cation for MS-related CNP and adds to the growing body of evidence for subcutaneous BoNT-A. Future research should include systematic methods for neuropathic pain assessment and outcomes of intervention. Ideally, this research should include a randomized control trial comparing BoNT-A injections to placebo injections, such as injection of subcutaneous saline. Furthermore, long-term outcomes on patients, including risks of side effects or decreased efficacy with multiple injections, should be considered and studied. At present, there are no studies that examine if the use of subcutaneous BoNT-A leads to underlying muscle weakness. Long-term randomized control trials on this treatment technique would allow for a better discussion of the risks and benefits of this procedure with the patient.

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