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Botulinum Toxicity Managed With Pyridostigmine Following Botulinum Toxin Injections for Bilateral Neurogenic Thoracic Outlet Syndrome: A Case Report

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Background: Botulinum toxin injections have been increasingly used in the treatment of different painful conditions, including thoracic outlet syndrome (TOS). Guidelines to manage adverse effects or toxicity from botulinum toxin injections in these cases are not well established.

Case Report: A female patient in her forties with bilateral arm pain secondary to bilateral neurogenic TOS (NTOS) presented to the pain clinic for botulinum toxin injections to the scalene muscles. Several hours after receiving the injections, the patient experienced dysphagia, hoarseness, and facial paresthesia suspicious for botulinum toxicity. She was administered pyridostigmine for symptom management and for approximately one month until symptom resolution.

Conclusions: To our knowledge, this is the first case report to discuss the presentation of botulinum toxicity and its management following botulinum toxin injections for pain relief in bilateral NTOS. Botulinum toxicity may be managed with pyridostigmine with some benefit, but further research is needed to establish guidelines.

Key words: Botulinum toxin injection, botulinum toxicity, pyridostigmine, thoracic outlet syndrome

BACKGROUND

Thoracic outlet syndrome (TOS) consists of a group of complex neurovascular conditions localized to the upper extremity due to compression of the brachial plexus (BP), subclavian artery, or subclavian vein (1-3). TOS is distinguished by the dominant anatomic structure involved; however, neurogenic TOS (NTOS) comprises over 95% of TOS cases in which the BP C5-T1 nerve roots are impinged most commonly between the anterior (AS) and middle scalene (MS) muscles and following neck trauma (1,3,4). The most reported NTOS symptoms are pain at rest (87%), paresthesia in the upper extremity (66%), and impaired strength (55%) that are exacerbated by postural elevation of the upper limbs (3,5). Conservative management, including neck and shoulder stretches, physical therapy, simple analgesics, and muscle relaxants, are first-line treatments for NTOS (4,6,7). If symptoms persist, anesthetic agents, steroids, and botulinum toxin type A (Botox, Allergan Corp, Irvine, CA) have been used for short-term relief (2,8). Rarely, scalenectomy with possible first rib resection can be offered for surgical management (2).

Botulinum injections have increasingly been used for management of NTOS. The botulinum toxin functions as a neurotoxin that cleaves the SNAP-25 SNARE protein to decrease the transmission of acetylcholine into the neuromuscular junction (3). Injections are typically conducted using ultrasound, electromyography,

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fluoroscopic, or computed tomography (CT) guidance to target the AS and MS and pectoralis minor muscles (2,3,8-10). By targeting these involved structures, the botulinum toxin can temporarily reduce muscle tightness and relieve compression against the BP. Reports (8,10,11) have shown significant symptom reduction, especially regarding pain relief.

Head- and neck-related adverse effects of botulinum toxicity include fatigue, ptosis, diplopia, dysarthria, weakness, dry mouth, choking, dyspnea, and dysphagia (12-14). More severe complications of paralysis and anaphylactic shock have also been reported (12). There is a paucity of literature reporting complications of the botulinum toxin in the treatment of NTOS and there is no guidance on the management of botulinum toxicity following injections in NTOS. To our knowledge, this case report is the first to describe the presentation of botulinum toxicity and its management using pyridostigmine following botulinum toxin injections for the treatment of pain from bilateral NTOS.

CASE

The patient provided consent to discuss her care in this case report.

A female patient in her forties was referred to the pain clinic for "bilateral arm pain" after being diagnosed with bilateral NTOS by her vascular surgeon. Her symptoms started in 2016 when a heavy cabinet fell on her, resulting in right shoulder area pain. Magnetic resonance imaging (MRI) of the shoulder at that time was nonspecific, but suggested adhesive capsulitis. In 2017, she was involved in a motor vehicle collision resulting in bilateral shoulder area pain and paresthesia in the second, third, and fourth fingers. On physical examination, her symptoms were reproducible when lifting her arms above her head and she was tender in the supraclavicular fossae bilaterally. Cervical MRI was conducted and negative for other conditions that could present similarly, suggesting a diagnosis of NTOS. Due to a recent history of peptic ulcer disease, nonsteroidal anti-inflammatory drugs were not recommended. She also had experienced adverse effects with acetaminophen and tizanidine, and therefore was not amenable to other medications in those classes. We discussed the use of botulinum toxin injections to the AS and MS and pectoralis minor muscles, as well as the risks, benefits, and alternatives to this treatment. The patient agreed to proceed with the injections.

Upon presentation to our office, the patient reported persistent 7/10 pain on the Visual Analog Scale (VAS) located bilaterally in the neck, shoulders, and arms. Given that the pain was worse on the right, we discussed starting with the right extremity with a plan to inject the left side at a future visit. After informed consent was obtained, the botulinum toxin was reconstituted with preservative-free normal saline. The skin was prepped with chlorhexidine and under sterile ultrasound technique, the targets were visualized. Botox was then injected through a 25-G, 1-inch needle with the following dosages and locations using ultrasound guidance: 30 U into the right AS muscle, 30 U into the right MS muscle, and 40 U into the right PM muscle (Figs. 1 and 2). The procedure was tolerated well without complications. At her follow-up appointment 3 weeks later, the patient reported a 50% decrease in pain and received the same treatment on the left side. The patient experienced 3 months of pain relief without any adverse effects.

Three months after her initial procedure, the patient experienced recrudescence of her NTOS pain. She reported VAS 6/10, sharp and aching pain in the right neck and arm. She denied any changes in her medical status between appointments. After obtaining consent, chlorhexidine was applied. Under sterile ultrasound guidance and after negative aspiration, Botox was injected with the following dosages and locations on the right side: 20 U into the AS muscle, 20 U into the MS muscle, and 60 U into the PM muscle (Figs. 1 and 2). The patient tolerated the procedure well, but described a bitter taste several minutes afterward. She was discharged home stable and advised to call for any adverse events.

The following day, the patient reported a worsening of symptoms with first feeling a sore throat and globus sensation when swallowing solids. Later, she described coughing on liquids, difficulty swallowing solids, hoarseness, and paresthesia to her cheeks and chin bilaterally. She was advised to go to the emergency department (ED) for evaluation where she was given pyridostigmine 0.5 mg intravenous (IV) by an ED physician prior to our evaluation. A bedside swallow study was conducted with exam concerning for a wet quality to her voice; therefore, restrictive diet precautions were made. CT neck imaging was performed that showed no structural abnormality. Flexible fiberoptic nasopharyngeal-laryngoscopic examination by otolaryngology (ears, nose, and throat [ENT]) showed patent airways and no overt vocal cord dysfunction. The toxicologist felt that her presentation was most suggestive of botulinum toxic-

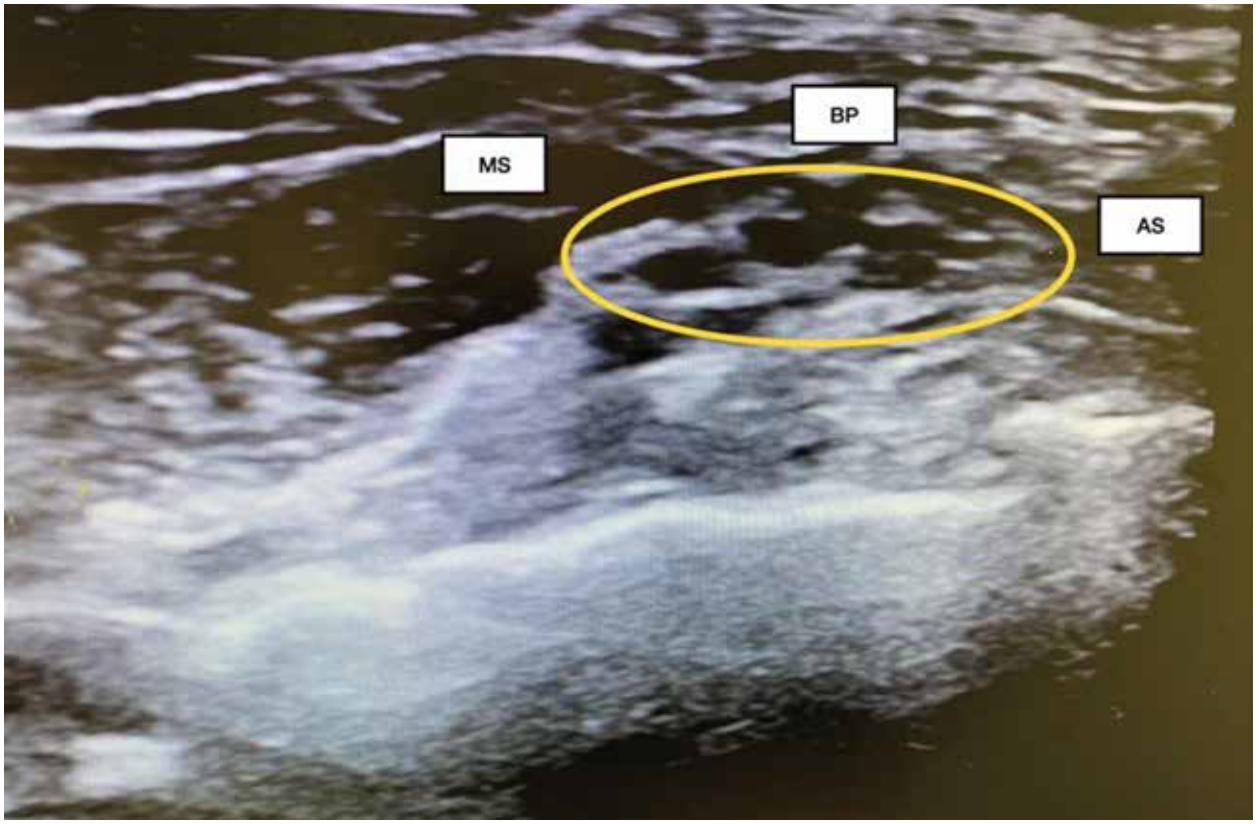

Fig. 1. Sonographic view of the middle scalene muscle (MS), anterior scalene muscle (AS), and brachial plexus (BP).

ity due to the onset of her pertinent symptoms shortly following the botulinum toxin injections. Although no known antidote for botulinum toxicity exists, the toxicologist recommended using pyridostigmine 60 mg orally 3 times daily vs 1-2 mg IV 3 times a day based on several case studies (13,14) and mechanisms to counteract Botox. Since she was on an oral diet restriction and already given pyridostigmine in the ED, she was admitted to the medicine floor for further evaluation.

On hospital day 1, the patient reported improvement in voice hoarseness and dysphagia, and was upgraded to a pureed diet; however, the patient complained of severe thirst, sialorrhea, and myalgias, which were thought to be secondary to the IV pyridostigmine. Utilizing pharmaceutical conversion data with 1 mg of parenteral pyridostigmine assumed equivalent to 30 mg orally, the pyridostigmine dose was converted to 30 mg oral 3 times daily to improve tolerability and compliance. On hospital day 2, the patient reported improved voice hoarseness and dysphagia with more tolerable side effects, so she was discharged the following day with pyridostigmine 30 mg oral 3 times daily.

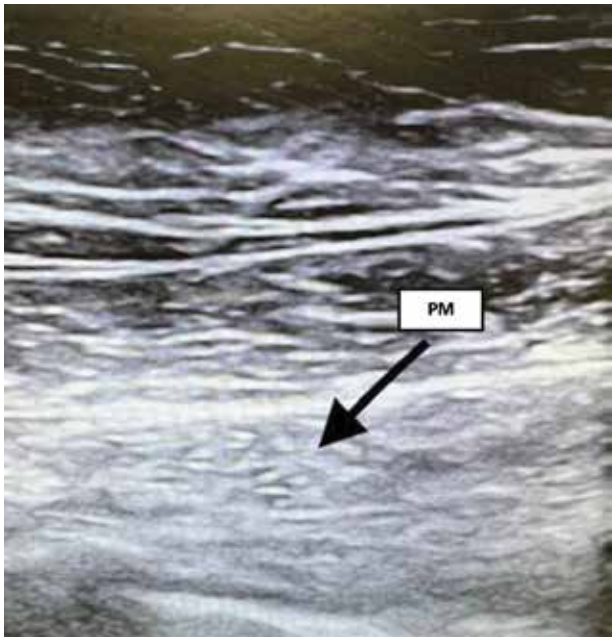

Fig. 2. Sonographic view of the pectoralis minor muscle (PM).

Two days after discharge, the patient continued to endorse improvement in hoarseness and dysphagia. However, she complained of intolerable adverse effects of pyridostigmine, including sialorrhea, diarrhea, mucus secretions, muscle spasms, and muscle cramps. During an outpatient ENT visit, videofluoroscopic swallowing study demonstrated only mild oropharyngeal dysphagia and swallowing discoordination, so she was recommended for diet upgrade to regular consistency with thin liquids with instruction on swallow techniques. Six days after discharge, the patient self-tapered her pyridostigmine dose to 30 mg in the morning, 15 mg in the afternoon, and 30 mg at bedtime due to complaints of intolerable sialorrhea. She continued to complain of mild globus sensation and numbness while swallowing and facial paresthesia due to residual botulinum toxicity. The patient was encouraged to continue pyridostigmine 30 mg 3 times daily.

Nine days after discharge, the patient developed a nonproductive cough at nighttime with chest tightness and difficulty sleeping. She was seen by urgent care for physical examination and chest x-ray with no acute pathology reported. She was thought to be experiencing an upper respiratory infection vs continued pyridostigmine side effects and was recommended over-the-counter dextromethorphan. We also advised her to taper the pyridostigmine to 30 mg in the morning, afternoon, and 15 mg at bedtime. Eleven days after discharge, the patient continued to report pyridostigmine side effects, so it was tapered to 15 mg in the morning, 30 mg in the afternoon, and 15 mg at bedtime. Eighteen days after discharge, the patient endorsed continued improvement in her dysphagia. Pyridostigmine was further decreased to 15 mg 3 times daily. At the one month follow-up, pyridostigmine was decreased to 15 mg twice daily with plans for further tapering and stopping over one week. After 1 month and 5 days from the inciting event, the patient reported no further dysphagia or hoarseness from the botulinum toxin. The patient is currently doing well without NTOS-related pain and continuing physical therapy.

DISCUSSION

Adverse effects of botulinum injections especially in the treatment of NTOS may be underreported and clear guidelines regarding the treatment of botulinum toxicity do not yet exist (12). Although Botox injections offer therapeutic efficacy in reducing muscle tightness and pain in NTOS, the botulinum toxin can cause adverse effects when it spreads beyond the injection site (15). Case studies (13,16) on adults with neurological and esophageal conditions who experienced head- and neck-related botulinum complications reported that toxic doses occurred anywhere between 1.8 U to 300 U dosages. The wide range of dosages at which harm can occur demonstrates the need for further research to prevent botulinum toxicity and alleviate adverse effects if encountered.

Pyridostigmine may mitigate the effects of botulinum toxicity by functioning as a reversible acetylcholinesterase inhibitor to increase acetylcholine availability in the neuromuscular junction (14). Previous case reports (13) describe managing botulinum toxicity successfully using pyridostigmine dosages of 60 mg oral 3 times daily, 300 mg oral twice daily, or a one-time 2 mg IV bolus, but with inconclusive time to relief. Most common side effects of pyridostigmine are diarrhea, diaphoresis, sialorrhea, respiratory secretions, muscle fasciculations, and cramps (14). As seen in our patient, these side effects severely affected compliance and increased discomfort (17). The possible severity of pyridostigmine side effects and lack of recommended dosing for reversing botulinum toxicity call further attention to establishing guidance.

Until guidance for the management of botulinum toxicity is established, it is still important to minimize its risks. During the treatment of NTOS-related pain, therapeutic doses have been observed below 100 U total and ultrasound-guidance can provide accurate needle placement to better prevent the botulinum toxin from spreading beyond the intended structure (2,18,19). It is also likely important to reduce the overall volume of injectate by decreasing the dilution ratio to prevent unintended spread. If botulinum toxicity is suspected, bedside ENT evaluation is important for excluding any airway obstruction or vocal cord dysfunction that may require emergent airway management. A videofluoroscopic swallow evaluation may also provide crucial information to reduce the risk of aspiration-related complications. These consultations followed by pyridostigmine IV then switching to oral administration with weekly symptom monitoring may provide patients with relief from botulinum toxicity while minimizing the adverse effects from pyridostigmine. Considering the need for further research, publication of this data is important to increase awareness of and begin establishing guidance for managing botulinum toxicity.

CONCLUSIONS

To our knowledge, this case report is the first to describe botulinum toxicity and its management following Botox injections for pain relief in bilateral NTOS. Ultrasound-guidance of Botox injections with doses at or below 100 U total can be preventative measures to prevent complications. Pyridostigmine may be important to reverse botulinum toxicity and prompt inpatient consultations may help to ensure patient safety, but further research is needed to establish recommended guidance.

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