Recent Advances for the Management of Raynaud Phenomenon Using Botulinum Neurotoxin A

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RAYNAUD PHENOMENON, A triphasic color response after exposure to cold or stress, is a vasospastic condition that often produces pain in the extremities, particularly the hands.[1,2] This article reviews the potential treatment of Raynaud phenomenon using *botulinum neurotoxin* A (BoNT-A).[1–8]

Raynaud phenomenon, if frequent and prolonged, results in digital ischemia, which can predispose the patient to occlusive disease with ulcers and gangrene. The primary treatment of Raynaud phenomenon is conservative and includes lifestyle modifications such as avoidance of cold conditions and tobacco. Available oral pharmacologic medications include calcium channel antagonists (the gold standard), endothelin antagonists, phosphodiesterase-5 inhibitors, antioxidants, and statins.[2] These drugs either modulate abnormal vascular reactivity or prevent occlusive events by targeting the complex interplay of vascular, endothelial, neural, and intravascular contributors to Raynaud phenomena.[1,2,4] The systemic administration of these medications is limited by efficacy, side effects, and polypharmacy concerns.[1,2,4] If conservative management fails, surgical intervention includes sympathectomy with or without arterial reconstruction.[1] Because surgery has attendant morbidity and is technically demanding, alternative local treatments are desirable.

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Based on preclinical data and limited case series, the palmar injection of botulinum toxins has been described to treat refractory Raynaud phenomenon with nonhealing ulcers or pre-gangrene. The BoNT-A cleaves synaptosomal-associated protein-25 (SNAP-25), thereby preventing vesicular fusion and neurotransmitter release from axon terminals into the synaptic cleft.[9] Efficacy is theoretically attributed to 2 potential mechanisms: (1) modulation of abnormal adrenergic innervation, with a decrease in abnormal shunting and maximization of nutritional perfusion and (2) reduction of pain through antinociceptive pathways, as BoNT-A can theoretically decrease nociceptive pain by reducing glutamate, substance P, and calcitonin gene-related peptide. These two mechanisms produce a de facto sympathectomy.[1–8]

The BoNT-A treatment can be used for debilitating, refractory Raynaud symptoms, including ulcers and existing gangrene. If a patient is allergic to BoNT-A or the pharmacological vehicle (normal saline without preservative), its use is contraindicated. Relative contraindications are failure to respond to previous injections, difficulty tolerating the resultant anhidrosis, and infection (cellulitis, purulent drainage) at the injection sites. Pretreatment evaluations can determine whether BoNT-A rather than surgical intervention has the potential to benefit the patient. In particular, patients with refractory pain without ulcerations can have Doppler ultrasound assessment, digital brachial indices, or microangiography. If the patient has refractory pain with ulceration, the physician might consider arteriography to determine whether the occlusive disease is repairable. The goal of preoperative studies is to determine whether the vascular disease causing the Raynaud phenomenon is surgically reconstructable occlusive disease. If the disease is determined to be surgically reconstructable, surgery should be pursued, as opposed to BoNT-A injection.

Because limited studies of BoNT-A injections for the management of Raynaud phenomenon are available, the number of injections and a standardized technique have

not been established.[3–8] Although several botulinum toxins are approved by the Food and Drug Administration for human use, none are labeled for this indication; therefore, these injections should be considered experimental. Reconstituted BoNT-A is injected palmarly and subdermally into interstitial spaces contiguous to the neurovascular bundles. Based on preclinical data, spaced injections at 1-cm intervals from the base of the fingers and throughout the palm would optimize drug delivery, because the toxin is known to diffuse 1 to 2 cm. The injection technique is designed to deliver toxin to the interstitial fluid surrounding the neurovascular structures. Palmar injections are given at the level of or slightly proximal to the A1 pulley.[5] In addition, targeting the neurovascular bundles at several alternative anatomic locations can be considered based on clinical presentation.[3] Regional blocks might also be considered because BoNT-A injection can be painful. Injections can be repeated at 4- to 6-month intervals, if efficacious.

EDUCATIONAL OBJECTIVES

- List the medications available for treating Raynaud's phenomenon.
- State the possible mechanisms of actions for Botulinum A in Raynaud's phenomenon.
- Discuss the indications and contraindications for Botulinum A in Raynaud's phenomenon.
- Describe the method and location of Botulinum A injection in Raynaud's phenomenon.
- Summarize the results of Botulinum A in the treatment of Raynaud's phenomenon.

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A case report demonstrated that BoNT-A injection reduced pain and discomfort caused by Raynaud phenomenon as assessed by the visual analog scale.[7] Quantitative analysis using laser Doppler interferometry demonstrated increased superficial skin blood flow in the treated hand after injection.[7] Improvements in digit color, hand function, transcutaneous oxygen saturation, and increased cutaneous temperature are also reported.[3,5,8] The BoNT-A injection resulted in improved hand blood flow, as assessed by Doppler ultrasound.[5–7] In several studies, patients experienced healing of hand ulcerations, presumably due to improved extremity blood flow following injection.[3,5,6,8] The treatment effects of BoNT-A occurred within several days following injection and lasted approximately 4 to 6 months.[3–8]

Injection of BoNT-A for the treatment of Raynaud phenomenon has adverse consequences. Patients can experience pain at the injection site, which commonly resolved within a few days. Anhidrosis was not evaluated, but it almost certainly occurred and could complicate healing. Many patients experienced subjective hand weakness following BoNT-A injection, possibly from paresis of the intrinsic musculature[3–8]; however, assessment of pinch and grip strength with a dynamometer did not demonstrate a significant difference in strength before and after the injection.[3] The effects of BoNT-A are temporary and reversible. The reduction in muscle contraction force is expected to be reversible within 6 months after a single injection.[9] Systemic toxicity of BoNT-A or major adverse events were not observed or reported in any of the case series.[3–8] Long-term toxicity and complications of BoNT-A treatment remain unknown because randomized, placebo-controlled trials with sufficient follow-up have not been performed.

The use of BoNT-A for the management of Raynaud phenomenon is not approved by the Food and Drug Administration, and it is not labeled for this use; thus Medicare reimbursement is unlikely. With private insurance companies, the physician will have to obtain a case-by-case preauthorization. Typically, the cost of BoNT-A medication is US$500 to US$600 per 100-unit vial, in addition to professional costs for the visit and procedure. For billing purposes, the Current Procedural Terminology code is 64999 (unlisted code), and it requires a 10-day global period.

The BoNT-A mechanism of action has the potential to target multiple symptoms of Raynaud phenomenon,[1,2] decreasing pain and improving hand function.[3–8] Both a basic science study of the effect of BoNT-A on the microvasculature and a large, clinical prospective study are necessary to determine the future role of BoNT-A in the treatment of Raynaud phenomenon. The use of BoNT-A for the management of Raynaud phenomenon described in this review article must be considered an off-label use that is not approved by the Food and Drug Administration. The BoNT-A is a safe and effective pharmacological agent used in a variety of orthopedic applications[9] that might have a role in the minimally invasive management of Raynaud phenomenon.

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JOURNAL CME QUESTIONS

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What is the location of Botulinum A injection in Raynaud phenomenon that optimizes drug delivery?

a. Base of the fingers
b. Palm
c. 0.5-cm intervals from the base of the fingers and throughout the palm
d. 1.0-cm intervals from the base of the fingers and throughout the palm
e. 2.0-cm intervals from the base of the fingers and throughout the palm

What should the patient be told about the use of Botulinum A injection in the management of Raynaud phenomenon?

a. Experimental, but Food and Drug Administration (FDA)–approved use
b. Off-label use
c. Experimental, off-label, non–FDA approved use
d. Investigational use
e. Accepted application, FDA–approved use

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