Management of Vasospastic Disorders with Botulinum Toxin A

Allen L. Van Beek, M.D.
Paul K. Lim, M.D.
Andrew J. L. Gear, M.D.
Marc R. Pritzker, M.D.

Minneapolis, Minn.

Background: Surgical digital artery sympathectomy is indicated when medical management has failed to control rest pain, impending infarction of digits, or healing of ischemic ulcerations caused by profound vasospasm that is associated with other systemic diseases. After digital artery sympathectomy, recurrence or persistence of vasospasm may compromise hand function and ultimately result in amputation of all or portions of both lower and upper extremities.

Methods: The authors present a case series of 11 patients with vasospasm producing intractable rest pain, digital ulcerations, and digit infarctions that failed aggressive medical therapy and that were then treated by perivascular injections of botulinum toxin A (Botox). Before Botox injection, the level of pain, cutaneous temperatures, color, and ulcerations and infarctions were documented

Results: The authors' longest follow-up was 30 months. All patients reported highly significant pain reduction, 10 of 10 to 0 to 2 of 10, within 24 to 48 hours after injection, persisting for months after the injection. Nine of 11 patients with nonhealing ulcers spontaneously healed small ulcers and areas of infarction after surgical debridement. Two cases required small skin grafts. Nine of 11 patients reported decreased severity and frequency of vasospastic episodes.

Conclusions: Hand injection of botulinum toxin A appears to be an effective treatment for intractable digital ulcerations and rest pain in patients with severe vasospastic disorders. Because of the complexity of surgical digital artery sympathectomy along with its associated high risk of persistent symptoms, the authors conclude that the therapeutic use of botulinum toxin A injections represents an attractive alternative therapy. (*Plast. Reconstr. Surg.* 119: 217, 2007.)

Raynaud's phenomenon is defined as episodic vasospasm of the digital arteries initiated by cold exposure or stress.[1] Transient soft-tissue blanching is followed by cyanosis and subsequent reactive hyperemia, pain, and dysesthesias. Raynaud's phenomenon is either idiopathic, known as Raynaud's disease, or a secondary finding associated with diseases such as scleroderma, rheumatoid arthritis, lupus, occlusive arterial disease, neurovascular compression, hematologic abnormalities, occupational trauma, central nervous system disease, trauma-related abnormality such as reflex sympathetic dystrophy, and malignant disease.[2,3] When associated with another disease as a secondary finding, it is labeled Raynaud's syndrome.

The medical treatment of Raynaud's syndrome includes eliminating the use of nicotine and caffeine products, cold avoidance, protective garments, biofeedback, aspirin or dipyridamole to inhibit platelet aggregation, oral calcium channel blockers, topical nitrates, angiotensin-converting enzyme inhibitors, short-term heparin anticoagulation, and intraarterial administration of reserpine.[2] If conventional therapy remains ineffective in alleviating pain or improving healing of digital ulceration, parenteral administration of iloprost, a prostaglandin I_2 prostacyclin analogue, has been shown to decrease the incidence and severity of vasospastic attacks and promote healing of digital ischemic

From the Division of Plastic Surgery, Department of Cardiology, and Division of Heart Failure, Transplantation, and Investigational Therapeutics, Minneapolis Heart Institute Foundation, and Section of Cardiology, Department of Medicine, University of Minnesota.
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ulcerations.[4] When these methods of medical intervention fail, digit infarction and severe rest pain occur, and surgical intervention may be recommended. Digital artery sympathectomy, as introduced by Flatt in the 1980s, is still the procedure recommended for patients with Raynaud's syndrome with refractory digital ulcerations.[5] It can be used in conjunction with arterial reconstruction of proximal palmer arteries, and has been shown to be effective for a variety of digital artery vasospastic disorders. Unfortunately, the recurrence rate following digital sympathectomy in patients with connective tissue diseases results in recurrent and even persistent symptoms. In the event of severe chronic symptoms, amputation of infarcted portions of the extremity is often required.

Botulinum toxin A has broad clinical applications including wrinkle reduction, blepharospasm, torticollis, ocular strabismus, achalasia, hyperhidrosis, and migraines. Botulinum toxin A appears to exert its primary effect by blocking the release of acetylcholine vesicles into the synaptic space. The off-label use of botulinum toxin A injection for the treatment of vasospasticity disorders was reported by us in 2003 and is not widely practiced for the treatment of vasospastic disorders. The first patient in this series had botulinum toxin A injected for the treatment of palmar hyperhidrosis associated with an undifferentiated mixed connective tissue disorder. She noted that the pain associated with her Raynaud's syndrome was eliminated for 3 months. She also noted healing of painful and refractory superficial digital ulceration adjacent to her fingernails. On the basis of this serendipitous observation, we hypothesized that botulinum toxin A produced a digital artery smooth muscle neuromuscular blockade. The arterial vessel wall smooth muscles are innervated by sympathetic fibers that use norepinephrine as the mechanism of synaptic transmission. This report describes the use of botulinum toxin A in 11 patients with Raynaud's syndrome presenting with intractable rest pain, impending infarction, infarction, and ischemic ulceration that were refractory to conventional oral and parenteral therapy.

PATIENTS AND METHODS

Nine women and two men underwent botulinum toxin A (Botox; Allergan, Inc., Irvine, Calif.) toxin injection into the palm for soft-tissue ulceration of the digits in the setting of Raynaud's syndrome. The patients' ages ranged from 23 to 70 years (Table 1). All had an associated connective tissue disorder and other comorbidities (Table 1). Patient 1 developed symptoms associated with digital vasospasm during pregnancy, and treatment was deferred until after her delivery.

All patients failed to have sufficient alleviation of findings following standard pharmacologic interventions before Botox injection (Table 2). Patient 1 could not be treated with the usual pharmacologic agents in the categories listed because of her pregnancy. All of the other patients underwent multidrug therapy. Consultations on patients 4 through 11 occurred on an inpatient basis because of intractable rest pain and persistent ischemia despite intravenous prostacyclin therapy. All Botox-treated

Table 1. Patient Descriptions

Patient	Sex	Age (yr)	Presenting Ulcerated Digit	Associated Diagnosis	Medical History
1	F	42	Right middle	Undifferentiated MCTD	Myositis; right palmar hyperhidrosis; peripartum
2	F	44	Right small	MCTD	JRA, hypertension
3	F	23	Right index	MCTD	DM, hypertension
4	F	70	Right index	CREST	S/P finger amputation
5	F	61	Right middle, index Left index	Scleroderma, MCTD	Rheumatoid arthritis
6	M	62	Right middle, ring Left middle, ring	CREST	CAD, chronic renal failure
7	F	47	Right middle	CREST	
8	M	57	Left middle, ring, small	MCTD	Pulmonary hypertension, hemifacial atrophy syndrome
9	F	54	Right hand all digits Right great and fifth toes	Scleroderma	S/P partial amputation right index, middle fingers
10	F	49	Right, left hands all digits	MCTD	Pulmonary hypertension
11	F	50	Right fourth, fifth toes	Buerger disease	DM

F, female; M, male; MCTD, mixed connective tissue disorder; CREST, calcinosis cutis, Raynaud's phenomenon, esophageal motility disorder, sclerodactyly, and telangiectasia; JRA, juvenile rheumatoid arthritis; DM, diabetes mellitus; CAD, coronary artery disease; S/P, status post.

Table 2. Patient Medication Management

Patient	Vasodilators	Antiplatelet Agents	Narcotic Analgesics	Intravenous Prostacyclin
1	–	+	–	–
2	+	+	+	+
3	+	+		+
4	+	+	+	+
5	+	+	+	+
6	+	+	+	+
7	+	+	+	+
8	+	–	+	+
9	+	+	–	+
10	+	–	–	+
11	+	+	–	+

patients had severe pain, digital ulcerations, infected infarction, and discontinuation of intravenous prostacyclin therapy before Botox injections. Patients 4 through 11 received Botox injections during those hospitalizations. Patients 1 through 3 received injections on an outpatient basis.

Digital arteriograms or magnetic resonance arteriograms (Fig. 1) were obtained for all patients to exclude proximal radial or ulcer artery occlusion. In patient 2, intravascular arteriography with adenosine injection was performed 2 months before Botox injection, whereas in the other patients, high-resolution digital magnetic resonance angiography was performed using a 3-T magnet. In two patients, follow-up magnetic resonance angiographic images were obtained within 1 month of Botox injection. Surface temperature recording was performed under ambient room temperature conditions using digital thermistor recorders (Fig. 2).

Technique

One hundred units of Botox was reconstituted with 0.9% sodium chloride with preservative at a dilution of 6 to 11 cc per 100-U vial. Patients 1 and 2 received injections around the digital vessels of the affected fingers only. Patient 2 had injections of her fourth and fifth fingers with complete relief but presented 1 month later with severe ischemia to her adjacent index finger. At that time, injections to the radial aspect of that hand were performed that alleviated her symptoms. This experience led to a change in injection protocol to include all fingers with the initial injection; however, unless the thumb is symptomatic, it is not injected. Thumb ischemia for unknown reasons is uncommon compared with finger ischemia.

The remaining patients had 100 U of botulinum toxin A injected into each hand treated.

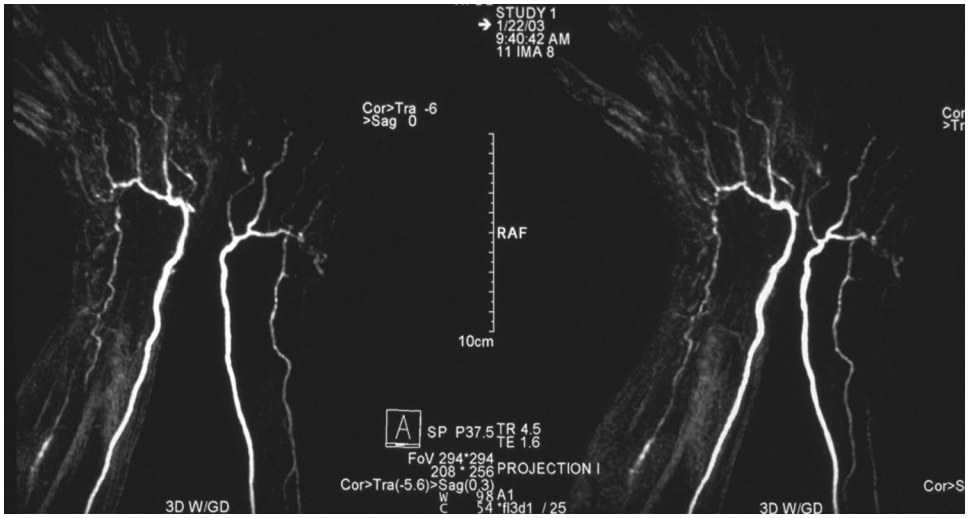

Fig. 1. Representative magnetic resonance arteriograms obtained to exclude proximal vascular occlusion that could produce ischemic digits rather than vasospasm.

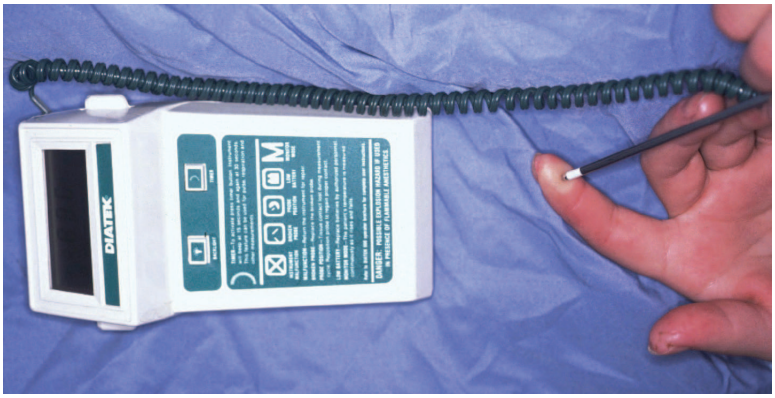

Fig. 2. Surface temperatures are recorded from the pulp of each digit using the technique shown. Excessive touch pressure and cold room temperatures should be avoided during recording.

Our protocol is to inject all the fingers and palm of the symptomatic hand with an equal distribution of Botox into each injection site. Only if the thumb is symptomatic will it be injected at its base. Each hand was injected with 100 U of Botox. With the exception of patients 1 and 2, when both hands were painful and ischemic, both hands were injected, with a total of 200 U being used, 100 U for each hand in the distribution outlined above. In addition to Botox injections, two patients required debridement of ulcers or infarcted tissue.

Targeted anatomy included the superficial palmar arch, common digital arteries, and proper digital arteries (Figs. 3 and 4). A 30- or 32-gauge needle is used to infiltrate the soft tissues around the arteries with the Botox solution. Through multiple injection sites, 8 to 12 U of Botox solution is injected into each of the eight or 10 areas shown in Figure 2. Injection adjacent to the common digital arteries and superficial palmar arch was made with the needle perpendicular to the palm and deep to the palmar fascia. The goal is to inject adjacent to the

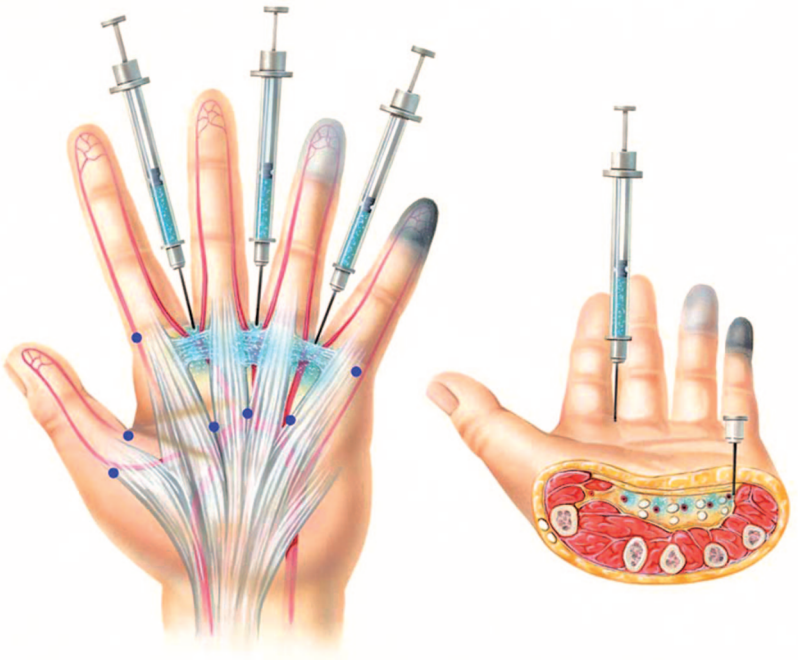

Fig. 3. Allergan Botox, 8 to 10 U, is injected into each site marked as a *red dot*. *Blue tinting* indicates the most concentrated areas of Botox diffusion.

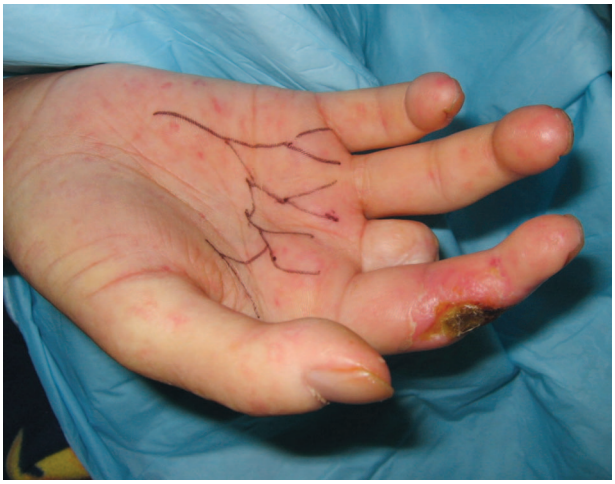

Fig. 4. This patient has lost digits secondary to ischemia and presently has an ulcer on the index finger. The vascular anatomy is visualized and the injections are planned along the proper and common digital arteries of the digits.

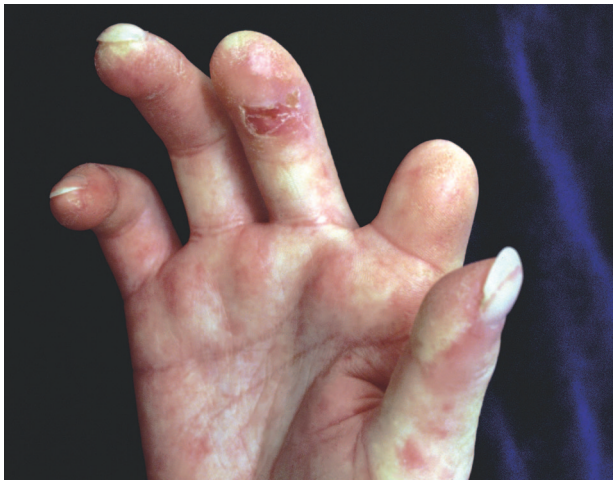

Fig. 5. The superficial ulcer on the middle finger healed by secondary intention following relief of vasospasm-induced ischemia.

vessels without injuring them. After injection, the palm and base of the digit is massaged gently for 30 seconds to help distribute the Botox throughout the region of injection.

RESULTS

The average follow-up was 9.6 months, and the longest follow-up was 30 months. All patients had relief of digital rest pain from 9 to 10 of 10 to a level of 0 to 2 of 10. They all reported decreased episodes of vasospasm and cyanosis. Small digital ulcerations all healed spontaneously. Large areas of infarction required debridement. None of the patients treated before obvious infarction had occurred required digit amputation, even when profound cyanosis, superficial ulcerations, and impending infarction where present. The skin temperature changes were measured in most of the patients treated both before and within 2 to 7 days after injection. Surface temperatures recorded in those patients demonstrated 1.0°C to 4.0°C increases in surface temperature. All patients reported that their fingers felt warmer within 48 hours of the injections.

Most patients presented with small superficial fingertip ulcerations (Fig. 3). Two patients presented with large areas of infarction, as demonstrated by Figures 5 and 6. They required debridement and skin grafting but healed by 3 months and remain healed. The ulcers on patients 1 and 5 healed in 1 month. Of note, patient 4, who had her right hand injected, returned for follow-up 2 weeks later having had such relief of her rest pain that she requested injection of her symptomatic, painful left hand (Table 3). Three patients reported mild "weakness" after being injected but had functional improvement because of less pain. None of the patients suffered any systemic complications related to the Botox. One patient died as a result of primary pulmonary hypertension 1 week after injection but reported symptomatic improvement in his hands.

Typical Case: Patient 2

A 44-year-old woman presented with dry gangrene at the tip of her small finger and her index and long fingers (Fig. 7). She had a history of progressively worsening digital ischemia, with tissue loss and pain despite aggressive medical management. Magnetic resonance angiography revealed that her large inflow vessels were patent (Fig. 1). Botox injections on the ulnar border of the hand relieved pain within 48 hours. Two months after the ulnar border Botox injection, the small finger ulcer had healed (Fig. 8). Progressive cyanosis of the index finger 1 month after initial treatment encouraged us to inject Botox into the radial side of the hand. Eight months later, Botox treatment was repeated to alleviate return of rest pain and superficial subungual ulcerations. For the past 30 months, she has required repeat injection every 5 to 8 months to prevent recurrent severe pain and ischemic cutaneous changes.

DISCUSSION

The pathophysiology of digital ischemia and ulceration in the context of Raynaud's syndrome involves both vasospasm and structural vascular alterations of arteries. The vasospastic compo-

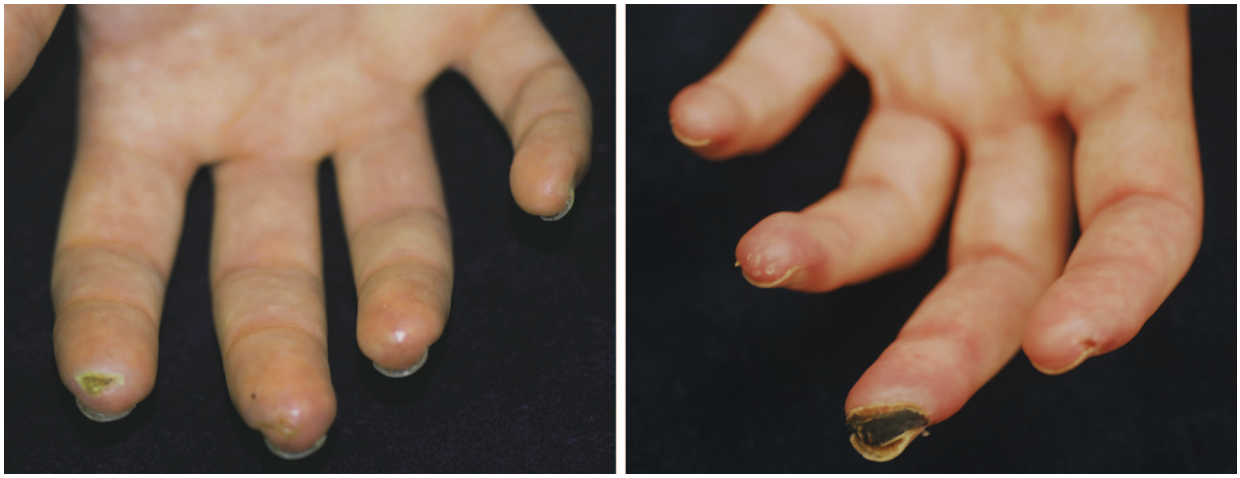

Fig. 6. After Botox injection, large areas of infarction require debridement and closure by amputation or skin grafting. It is our impression that injections improved healing times along with alleviating pain and frequent vasospastic episodes.

nent, termed Raynaud's phenomenon, was originally attributed to an exaggerated sympathetic nervous system response to cold.[6] In 1929, Lewis postulated a "local fault" within the digital artery itself.[7] Vasoconstriction occurs by cold-induced recruitment and amplification of α_2-mediated vasoconstriction in response to norepinephrine.[8]

Patients with Raynaud's phenomenon possess abnormal, overactive α_2 receptors.[9] Scleroderma patients are more sensitive to α_2-adrenergic agonists than normal individuals.[10] Flavahan et al. demonstrated that smooth muscle cells harvested from the small cutaneous vessels of patients with scleroderma possessed increased thermolabile α_2-adrenergic reactivity.[11] Histologic examination of small and medium arterial vessels in scleroderma patients demonstrates proliferative fibrous, concentric changes in the vessel media, and intima lesions that are associated with intravascular microthrombi.[12,13] The fibrous lesions may be progressive, resulting in complete luminal occlusion, and this finding is where microsurgical treatment on the digital artery surgery is directed.

Since its introduction by Flatt in 1980, digital artery sympathectomy in conjunction with vascular reconstruction has been used as a salvage procedure for patients with severe Raynaud's syndrome and digital ulcerations.[5] Digital sympathectomy produces improved blood flow in part through adventitial stripping of sympathetic fibers and removal of fibrous tissue from the media.[14] Wilgis, Koman, and others have modified digital sympathectomy.[14–17]

The use of surgical sympathectomy for Raynaud's phenomenon has met with mixed success. Ward and Van Moore performed digital sympathectomies on seven patients and noted ulcer healing in an average of 3.7 weeks.[18] Ulcer recurrence was observed in three patients.[18] Yee et al. reviewed the records of nine patients with collagen vascular disease who underwent digital sympathectomies.[19] All patients were asymptomatic postoperatively, but four subsequently went on to develop fingertip necrosis. More recently, McCall et al. demonstrated good results in four patients with scleroderma, and noted that repeat digital sympathectomy in one patient warded off a recurrence. This report introduced the value of a repeat surgical sympathectomy.

The use of Botox to create a chemical, digital sympathectomy for the treatment of digital ulcerations in patients with Raynaud's syndrome has not been previously reported. In March of 2004, Sycha et al. published a letter to the editor in the *European Journal of Clinical Investigation* describing two cases where Botox was used to treat Raynaud's phenomenon.[20]

The effect of Botox at the skeletal neuromuscular junction and its clinical applications have previously been described extensively, and the chemical denervation lasts several weeks to months and is dose dependent. Skeletal muscle functional recovery is predicated on the sprouting of new nerve terminals. Botox has been used in a variety of conditions pertaining to muscular spasticity, including torticollis, ocular strabismus, achalasia, and migraines.[21] Hyperhidrosis is also effectively treated by Botox by denervating sympathetic stimulation of eccrine sweat glands.[22,23]

A lesser known attribute of Botox, and one that is pertinent to this report, is the effect on autonomic and adrenergic nerves and vasomotor tone. Botox has been shown to prevent release of norepineph-

Table 3. Botox Management

Patient	Presenting Ulcerated Digit(s)	First Injection Botox Dose	Metachronous Disease	Second Injection Interval/Botox Dose	Third Injection Interval/Botox Dose	Fourth Injection Interval/Botox Dose
1	Right middle	100 U, right				
2*	Right small	100 U, right (ulnar side)	Right index	1 mo/100 U, right (radial side)	2 mo/100 U, left	8 mo/100 U, right; 100 U, left
3	Right index	200 U, right		11 mo/100 U, right	4 mo/100 U, right	
				100 U, left	100 U, left	
4	Right index	200 U, right	Left hand	1 mo/100 U, left		
5	Right middle	80 U, right				
	Right index	20 U, left				
	Left index					
6*	Right middle, ring	100 U, right				
	Left middle, ring	100 U, left				
7	Right middle	100 U, right				
8	Left middle, ring, small	100 U, left	Right index, middle	2 mo/60 U, right		
				40 U, left		
9	Right hand all digits	100 U, right hand	Right small (between second and third injections)	6 mo/80 U, right	1 mo/100 U, right	
	Right first, fifth toes	100 U, right foot		20 U, right foot		
10	Right, left all digits	100 U, right				
		100 U, left				
11	Right index, middle, ring	50 U, right				
	Right fourth, fifth toes	50 U, left				
		100 U, right foot				
		100 U, left foot				

*Underwent sharp debridement of ulcers.

rine at the neuromuscular junction.[24] Morris et al. demonstrated that Botox prevents sympathetic vasoconstriction of the vascular smooth muscle of guinea pig uterine arteries by blocking exocytosis of norepinephrine vesicles at the neuromuscular junction.[24] Cold-induced vasoconstriction, which is aberrant in patients with Raynaud's syndrome, is mediated by recruitment of specific α_2 receptors (α_{2c}). The signaling pathway leading to vasoconstriction used by α_2 receptors in vascular tissue involves phospholipase D, tyrosine kinase pp60^{src}, and the low-molecular-weight protein RhoA.[25] Phospholipase D activity is completely blocked by Botox.[25] Similarly, antibodies directed against RhoA diminish phospholipase D levels.[25] Interestingly, a Rho kinase has also been linked to selective translocation of α_{2c} receptors from the Golgi complex to the plasma membrane in response to cold.[26] Thus, Botox may possess a dual action: inhibition of vasospasm by blocking cold-induced vasoconstriction and by preventing recruitment of α_2 receptors to vascular smooth muscle in cold conditions. Qualitative anal-

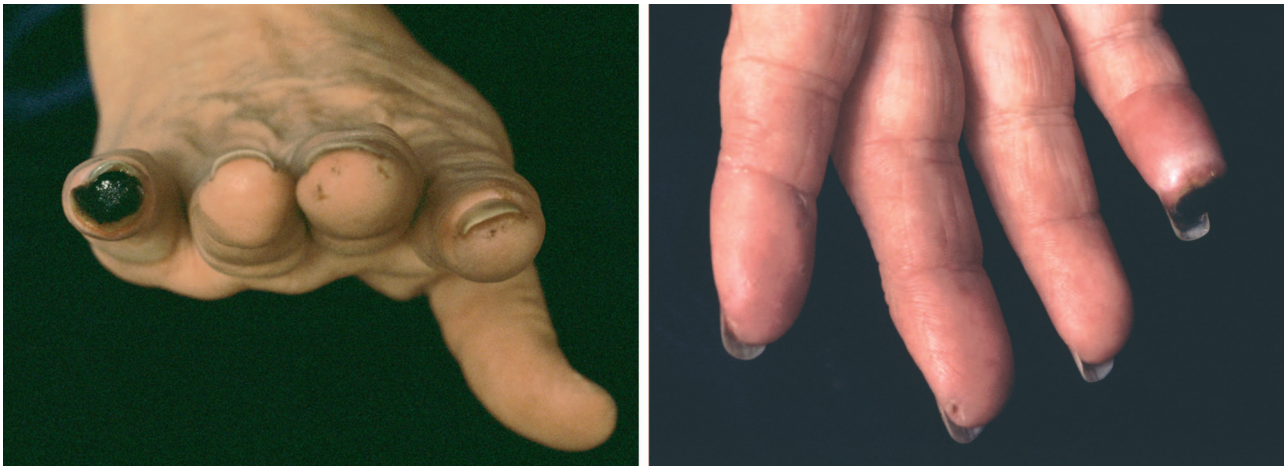

Fig. 7. Patient 2 before injection of the ulnar border of the hand. The small finger has distal tip infarction.

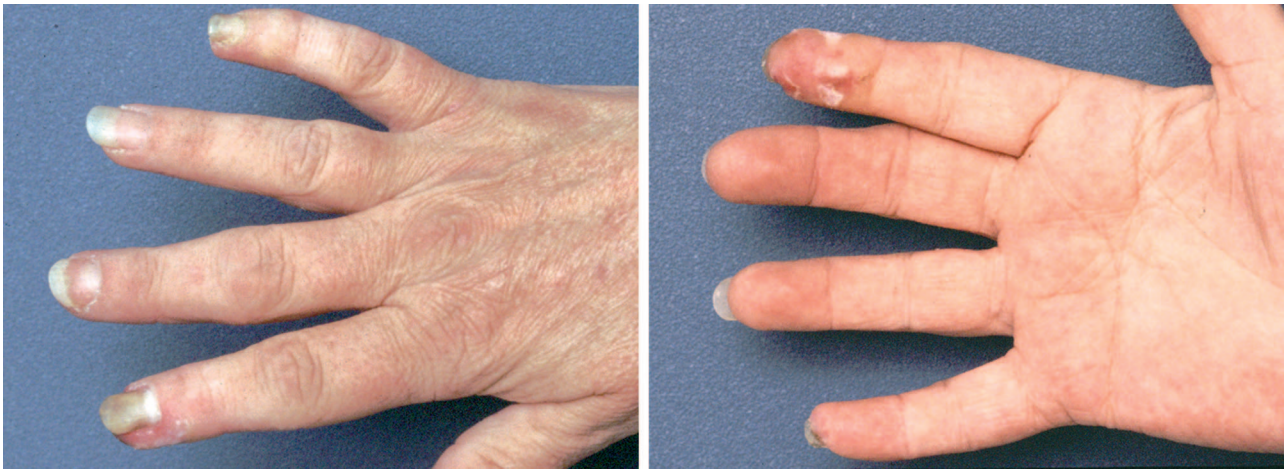

Fig. 8. Photographs of patient 2 obtained 3 months after the first Botox injection showing that the small finger has healed. One month after the first Botox injection, the radial side also became ischemic, and the index finger developed superficial infarction and skin loss. Botox injections at that time reversed ischemia; the photograph on the right shows early healing of those ulcerations. The index finger healed without debridement.

ysis of before and after, digital, high-resolution, magnetic resonance angiograms obtained with a 3-T magnet in six of our patients demonstrated no macrovascular alterations, suggesting that the therapeutic effects of Botox injection are exerted at the microvascular level. The exact mechanism of action explaining why Botox is effective in preventing vasospasm still requires additional experimental and clinical data. An explanation for the early onset of relief from pain and ischemia in some of our patients after injection is unknown. We speculate that it could be related to Botox causing a direct smooth muscle effect, a chemical sympathetic nerve conduction block, an afferent nerve block, or still unknown effects of botulinum toxin.

We previously reported Botox as a novel treatment for severe digital vasospasm. However, with additional experience, Botox is seemingly the indicated treatment for patients previously considered for surgical sympathectomy. Nine of 11 patients in this series had resolution of rest pain, diminished cold intolerance, decreased frequency of vasospastic attacks, and healing of digital ulcerations. In five patients with longer follow-up, repeat injections have been required within 3 to 8 months. All patients had subjective increase in finger warmth, and cutaneous surface pulp temperature increase of 1.0 to 4.0°C occurred in seven patients. Our digital temperature measurements were obtained in various ambient conditions, and a

more controlled recording environment would provide more useful data.[16] A more useful quantitative measure of blood flow such as laser Doppler flow before and after injection would be more quantitative.[20] No systemic effects were noted; relief of severe pain allowed individuals to increase the use of their hands.

Like the surgical form of digital sympathectomy, the location, dosage, and timing of Botox injection require further study. It is important to ensure preinjection proximal vascular patency, and if proximal vascular inflow is insufficient, it needs to be corrected as part of the treatment plan.

There are obvious weaknesses in this clinical study. Most of our patients were hospitalized for aggressive medical management of their ulcerations, impending infarction, and pain management that included intravenous prostacyclin. Prostacyclin has been shown in a prospective, randomized study to improve digital ulcerations by 50 percent.[4] However, experience from our group resulting from over 100 episodes of treatment with parenteral prostacyclin for refractory digital ulceration has suggested that the outcome of treatment can be predicted by the early relief of pain and improved perfusion within 72 hours. All treated patients in this group with the exception of the patient with pregnancy-associated onset of symptoms failed to respond to prostacyclin therapy within 48 to 72 hours and then underwent treatment with Botox.

A well-known and significant placebo effect exists among patients with less severe Raynaud's phenomenon, and for statistical assessment, prospective studies are necessary. However, the effectiveness of Botox in healing ulcers and decreasing pain in our series raises the ethical dilemma of denying treatment when patients are faced with finger amputation. A prospective, controlled, randomized study is needed, and we are presently planning such a study.[20] Finally, Botox has potential applications for other vasospastic conditions of the hand, including frostbite, regional pain syndrome, reflex sympathetic dystrophy, vasopressor-induced digital ischemia, and extravasation injuries.

CONCLUSIONS

A series of patients suffering from severe Raynaud's syndrome are presented, and the injection of Botox appears to inhibit vascular spasm and the frequency of attacks, decrease ischemic rest pain, and promote healing of ischemic digital ulcerations and prevent the need for surgical sympathectomy. In our case series, all patients had profound ischemia of the digits associated with secondary causes of Raynaud's phenomenon and, when treated with Botox, had substantial improvement in symptoms and findings.

Allen L. Van Beek, M.D.
7373 France Avenue South
Edina, Minn. 55435
lavb@vanbeekmail.com

DISCLOSURE

None of the authors has any financial interest in the products, devices, or drugs mentioned in this article.

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