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Research

Botulinum Toxin in the Treatment of Vasopressor-associated Symmetric Peripheral Gangrene

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Summary: Symmetric peripheral gangrene (SPG) affects peripheral tissues of critically ill patients and can have severe disfiguring and debilitating effects. It can occur in the setting of multiple conditions, and it is associated with the use of vasopressors. There are no evidence-based treatments available for patients who develop SPG. Botulinum toxin has emerged as a potential therapy in vasospastic disorders, and we hypothesized that it may be used in the treatment of tissue ischemia in critically ill patients on vasopressors. We present a case of a patient who developed vasopressor-associated SPG and who experienced complete resolution after local injection with botulinum toxin. While the action of botulinum toxin on skeletal muscle is best understood, it has also been demonstrated to attenuate the release of multiple vasoconstrictive factors that impact vascular smooth muscle and modulate calcium and nitric oxide. These effects may result in vasodilation and improvement of cutaneous ischemia when injected locally. Clinicians may consider this local therapy in the treatment of vasopressor-associated symmetric peripheral gangrene. *(Plast Reconstr Surg Glob Open 2021;9:e3582; doi: 10.1097/GOX.0000000000003582; Published online 21 May 2021.)*

INTRODUCTION

Symmetric peripheral gangrene (SPG) affects critically ill patients and involves the distal limbs, nose, ears, scalp, and genitalia.[1] It is associated with multiple clinical conditions, including sepsis, cardiogenic shock, malignancy, and connective tissue and hematologic disorders.[2] SPG occurs in the setting of systemic microthrombosis and dysregulated hemostasis, and it is associated with disseminated intravascular coagulation.[1,2] The use of vasopressors contributes to the development of SPG.[3–5] In patients who survive, the tissue loss of SPG can be debilitating and disfiguring. There are no systematic analyses demonstrating efficacy for any pharmacologic treatment to prevent or reverse SPG.[6,7]

Botulinum toxin (BT) has emerged as a promising treatment modality in vasospastic disorders such as Raynaud's phenomenon.[8] In animal models of flap surgery, BT has been demonstrated to improve flap survival, blood flow, vessel diameter, and angiogenesis.[9] It has also recently been recommended as a treatment option for vasopressor- and trauma-induced digital ischemia.[4,10,11] We present a case report to highlight the potential use of BT in the treatment of vasopressor-associated SPG.

CASE REPORT

The patient was a 29-year-old woman with a history of systemic lupus erythematous, lupus nephritis, and Raynaud's phenomenon who presented to the hospital in septic shock with disseminated intravascular coagulation. Skin examination was significant for duskiness of the hands, feet, and nose, and a petechial rash over the nose, tongue, and perioral area. She required continuous infusion of norepinephrine (30 mcg/min), vasopressin (0.03 unit/min) and epinephrine (1 mcg/min) and continuous renal replacement therapy for acute kidney injury. Blood cultures grew *Streptococcus pneumoniae,* and she was treated with antibiotics.

She remained on vasopressor support on hospital day 2 (norepinephrine: 4 mcg/min, vasopressin: 0.04 unit/min, epinephrine: 1 mcg/min). By hospital day 3, her nasal tip displayed significant ischemic changes. Her nose was injected with 50 units of botulinum toxin type A (Brand: Botox, Allergan, Ireland) in 10 divided doses at the junction of unaffected and violaceous skin (Fig. 1A). All injections were performed at the same time, spaced evenly along the demarcating skin. Pressor requirements decreased to vasopressin only (0.04 unit/min) on hospital day 4, and she was weaned from vasopressin on hospital

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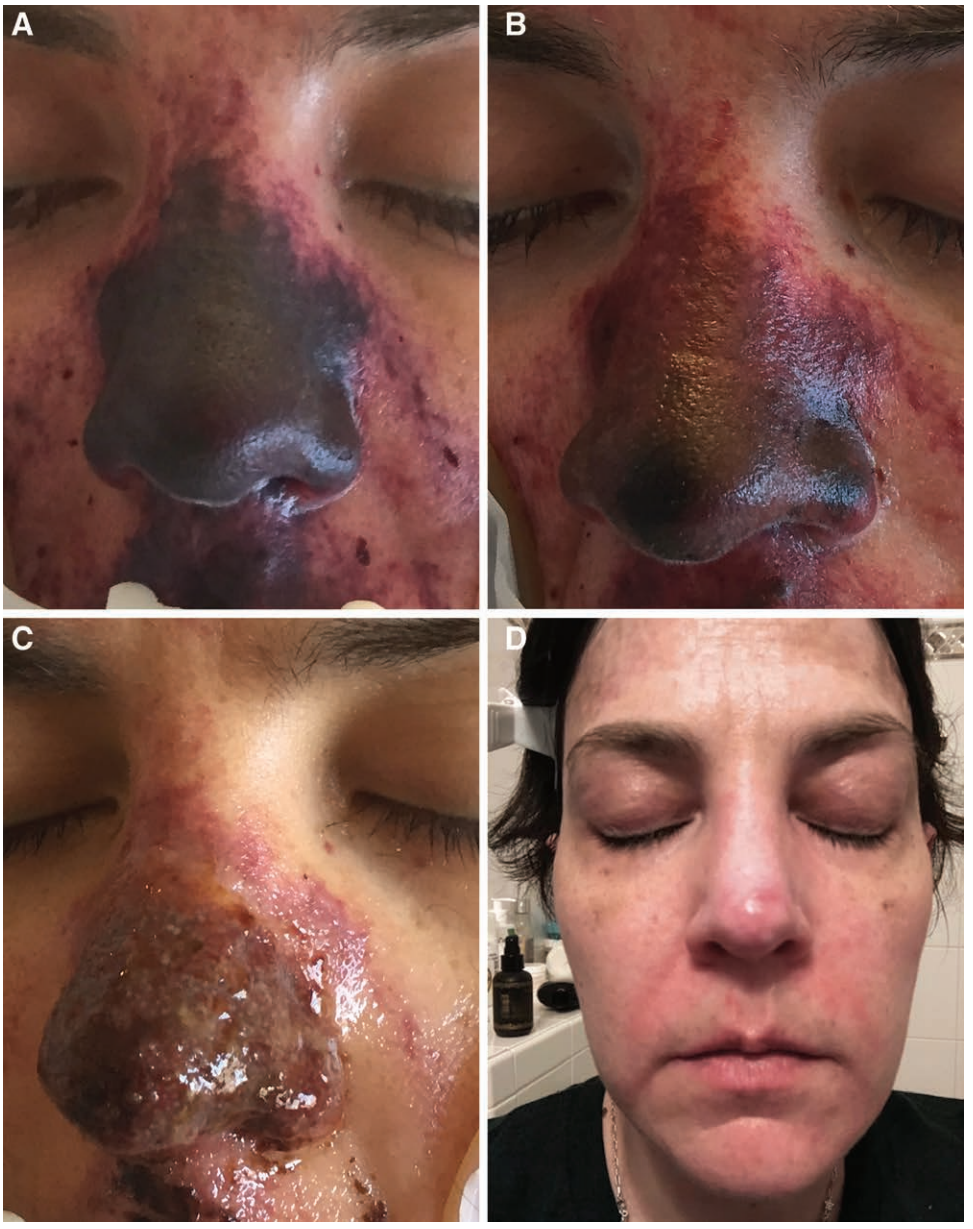

Fig. 1. Botulinum toxin injection in a patient with vasopressor-associated ischemia of her nose. A, Hospital day 3; 50 units of botulinum toxin injected into the nose. The patient continued to require norepinephrine and vasopressin. B, Hospital day 5; 2 days after botulinum toxin injection. The patient only required vasopressin. C, Hospital day 9; 6 days after botulinum toxin injection. The patient was off of vasopressors. D, Follow-up result at 3 years.

day 5. On hospital day 6 (3 days after injection), the color of the nose improved from deep purple/black to light purple/red with areas of necrosis at the distal tip and bilateral ala. At this time, all fingertips and toes had progressed to necrosis. From hospital day 6 to 10, she required intermittent vasopressor support. Over the subsequent weeks, the nasal skin fully healed (Fig. 1B, D). All fingers were amputated before hospital discharge, and she had a local flap to avoid a proximal amputation of the right thumb at the metacarpophalangeal joint. Both lower limbs eventually underwent below knee amputation with concurrent targeted muscle reinnervation.

DISCUSSION

Here, we present a report of the clinical potential of BT in the treatment of vasopressor-associated SPG. The causative agent was septic shock due to *Streptococcus pneumoniae* infection, as the dusky appearance of her face and extremities was noted before vasopressor administration. SPG was then likely worsened due to vasopressors. A significant response was observed within days of botulinum toxin therapy, with eventual complete resolution of ischemic skin changes. Peripheral tissues that did not receive BT underwent a continued evolution toward frank necrosis.

The off-label use of BT has been demonstrated to improve pain, oxygen saturation, and blood flow in Raynaud's phenomenon.[8] Vascular smooth muscle is innervated by sympathetic fibers that release norepinephrine for synaptic transmission.[12] Botulinum toxin A inhibits exocytosis of acetylcholine into the synaptic cleft via cleavage of the SNAP-25 protein in the SNARE complex.[13,14] However, there is evidence that BT has an inhibitory effect on other signaling mechanisms.[15] It has been shown to attenuate the release of norepinephrine in a guinea pig vascular model via SNAP-25 cleavage.[16] BT has also been shown to inhibit transmission of neurotransmitters such as substance p, glutamate, and calcitonin gene-related protein, thereby decreasing adrenergic output.[8] In addition, the vasoactive mechanism of BT may be related to its modulation of calcium and nitric oxide.[17] Recent research suggests that BT decreases calcium sensitization and affects signaling pathways involving endothelial nitric oxide synthase and cyclic guanosine monophosphate.[18] This mechanism is supported clinically by the use of BT to prevent reperfusion injury, which is in part caused by increased calcium sensitization and vasoconstriction.[19,20] BT mediates vasodilation in smooth muscle through multiple mechanisms, and it appears to create a chemical effect similar to sympathectomy.

The use of vasopressors compounds the risk of ischemia in patients with disseminated intravascular coagulation by inducing vasoconstriction in the setting of underlying hematologic dysregulation.[3,5] BT may alleviate the local effect of vasopressors to improve tissue oxygenation. A prospective trial was initiated in 2011 to study the use of BT in vasopressor-induced digital ischemia, although it was terminated due to low accrual.[21] This potential treatment has distinct advantages. It is injected locally, so there is reduced risk of the systemic side effects associated with intravenous medications. BT also does not cause permanent tissue damage, in contrast to obliterative sympathectomy. BT may reduce the risk of disfigurement and amputation from SPG, and it could be useful when a patient is developing SPG and may remain on vasopressor support for a prolonged period.[4] High-quality studies are warranted to investigate this potential use, although conducting such studies is difficult due to the low incidence and high mortality of the condition.

It may be argued that the ischemia of the nose would have resolved without any intervention when the inciting factors were removed. The face is more vascularized than the digits, which could theoretically explain why the extremities were lost but the nose ischemia resolved. However, it is unlikely that the nose ischemia would have resolved without any sequelae. The natural course of SPG is permanent tissue loss, and the majority of patients require amputations.[5,6] While there have been few case reports of SPG resolution,[22,23] the extent of SPG in those cases was limited to digital tip necrosis, not extensive necrosis of all 4 limbs and face, as seen in this case. In addition, we believe the reduction in vasopressors did not play a large role in the resolution of the nasal ischemia, as the effect would have also been seen in the limb ischemia, which consistently progressed even after vasopressors were stopped. It could also be argued that her ischemia was due to an exacerbation of her underlying systemic lupus erythematosus; however, it is unusual for rheumatologic disease to cause this level of ischemia and frank necrosis of all 4 limbs.

In retrospect, we wish that we had injected Botox into all of the regions of ischemic tissue on day 2. At the time of initial evaluation, all limbs had non-blanching skin, but only 1 small finger fingertip had an area of full-thickness necrosis. As we expected the majority of the limb tissue to survive, we elected to observe. There was a lower threshold to inject her nose, as the downsides of BT injection are few, and complete loss of the nose presents a significant reconstructive challenge. We believe the ideal timing of BT injection is when irreversible signs of necrosis develop, but further study is necessary. In this case, phentolamine was not considered, as it is more commonly used for ischemia related to local vasopressor extravasation, not complications related to systemic vasopressor administration.[11]

This report demonstrates the effect of BT in vasopressor-associated SPG. Future prospective studies are needed to confirm the effects observed here. However, given the established safety of botulinum toxin and potential benefit of salvage, we recommend that clinicians consider BT therapy in the management of vasopressor-associated peripheral ischemia.

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