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Botulinum toxin type A in the treatment of Raynaud's phenomenon

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Abstract

Raynaud's phenomenon is a vasospastic disorder clinically characterized by cold or stress-induced discoloration of the skin, pain and ulcers of the fingers or toes. Although this phenomenon might be self-limiting, there is a subgroup of patients requiring a therapeutic approach. The majority of patients do well on conservative measures; however, there is also a subgroup requiring systemic treatment. The efficacy of these systemic treatments is currently not thoroughly investigated. Furthermore, no uniform guidelines exist regarding the choice for a treatment option. In the past several years, several reports have shown the benefits of botulinum toxin for the treatment of Raynaud's phenomenon. In this case series, we report our experience with botulinum toxin type A in the treatment of Raynaud's phenomenon.

KEYWORDS

botulinum toxin, pain, Raynaud's phenomenon, vasospastic

1 | INTRODUCTION

Raynaud's phenomenon characteristically presents itself with triphasic discoloration of fingers and toes resulting from vasospasm. The vasospasm of the digital arteries may occur spontaneously or after exposure to cold or stress. Secondary Raynaud's phenomenon may be a secondary sequela of associated conditions such as systemic sclerosis. Pain is frequently an accompanying symptom altering the quality of life of many patients. Minor cases can be treated with general measures such as changes in lifestyle and heated gloves. More serious patients need systemic medication.[1] However, some are refractory to all prevalent therapies.

Botulinum toxin (BTx) type A (BTx-A) is a polypeptide which is produced by the bacteria *Clostridium botulinum*. Its main mechanism of action is inhibition of acetylcholine release in the peripheral nerve ending at the level of the motoric end plate. Through the cleavage of synaptosomal-associated protein 25 of acetylcholine vesicles, the light chain of BTx blocks the release of acetylcholine causing muscle paralysis.[2] Within the field of dermatology, BTx is mainly used for aesthetic treatments and management of focal hyperhidrosis. However, many off-label indications, especially for dermatological diseases, have been reported in recent years. Application of BTx has been reported in the management of keloids, hypertrophic scars, alopecia androgenetica, sweating-related disorders (eg, Hailey-Hailey disease) or pain- and itchness-related disorders (eg, notalgia paresthetica).[3,4] In this, report we present our experience with BTx injections in three debilitating cases of Raynaud's phenomenon.

2 | CASE SERIES

2.1 | Case 1

A 50-year-old nonsmoking female with inflammatory arthralgias, Raynaud's phenomenon, nail fold capillaritis, leukopenia, increased complement activation and positive autoantibodies (ANF or

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Antinuclear factor), was diagnosed as unclassified connective tissue disease. Raynaud's symptoms were provoked by cold, but were also present during summer. Despite twice daily (2dd) 30 mg nifedipine and 400 mg hydroxychloroquine and strict adherence to the advised lifestyle, she experienced 30 episodes at both hands daily. This had a tremendous impact on her daily activities. Treatment consisted of subcutaneous injections in the web spaces of digits 2 to 5 on both hands near the metacarpophalangeal (MCP) joints (Figure 1). Thirty-two units of BTx-A were injected in eight injections on each hand (64 units in total on two hands). At follow-up after 1 week, she revealed complete absence of symptoms. Her pain score was reduced from 8 to 0.

2.2 | Case 2

A 25-year-old female with calcinosis cutis, digital ulcers and anticentromere antibodies was diagnosed with systemic sclerosis. She had puffy hands and symptoms of severe Raynaud's phenomenon. She smoked 10 cigarettes per day. She was on medication with 2dd nifedipine 30 mg and bosentan 125 mg. Prior to this, she had intravenous iloprost. She received the same treatment as case 1. No effect was noted at follow-up after 1 and 2 weeks.

2.3 | Case 3

A 23-year-old female with morphea en coup de sabre was diagnosed with primary Raynaud's phenomenon. She exhibited 25 episodes daily with a pain score of 7. She received no systemic medication. We treated her in the same way as in case 1, but the exception was that her left (nondominant) thumb was also treated both on the medial and lateral sides. At follow-up after 1 week, the patient was completely free of symptoms. She was able to place her hand in a bowl of ice without noticeable vasoconstriction afterwards.

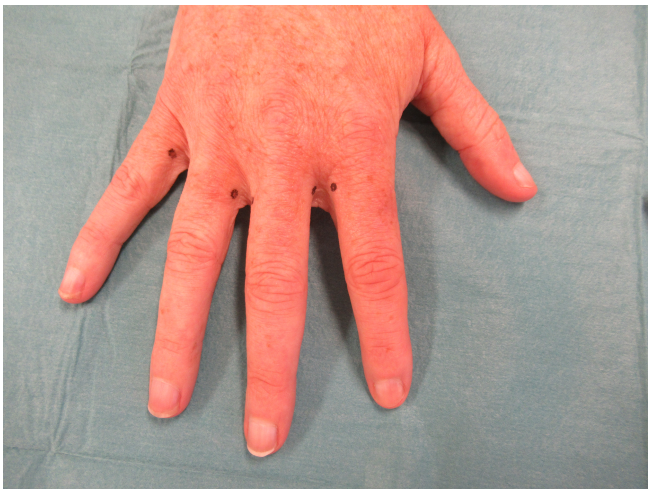

FIGURE 1 Subcutaneous injections in the web space of digits 2 to 5 on both hands near the metacarpophalangeal joints

3 | DISCUSSION

No uniform strategy exists for the treatment choice in patients with more severe Raynaud's phenomenon. Most patients are currently treated with calcium antagonists. Other modalities include phosphodiesterase inhibitors, angiotensin II receptor antagonists, selective serotonin reuptake inhibitors or intravenous iloprost.[1,5] BTx-A injections may be an alternative in cases who do not respond to the general systemic therapies.

In the three cases with Raynaud's phenomenon presented in this current report, BTx-A injections in the interdigital web spaces had no effect in one, but showed a spectacular improvement in the other two. The positive effects of treatment persisted for 3 months in our patients. No side effects were noted.

The result of our study regarding the beneficial effects of BTx concurs with findings of the current literature. After the first case in 2004,[6] several studies reported a reduction of pain and frequency of attacks.[7-12] Also, fingertip ulcers have been found to heal after BTx injections.[2,8,10,13] However, these reports are mainly based on case reports or case series. Van Beek et al[8] reported a case series of 11 patients with connective tissue disorder-related Raynaud's phenomenon that were treated by perivascular injections of BTx-A. Nine out of 11 patients reported an improvement in the frequency and severity of vasospastic episodes. Neumeister et al[2] reported a reduction of pain in 16 out of 19 patients with Raynaud's phenomenon who were treated with 50 to 100 units of BTx. Thirteen of these patients reported immediate relief of pain. Fregene et al[10] reported healing of fingertip ulcers in 11 of 23 patients after completion of the treatment course with BTx-A with average time to healing of 9.5 weeks. In a report of five Japanese patients with systemic sclerosis, digital ulcers in all patients healed within 12 weeks after injection.[11]

The only performed randomized, double-blind, placebo-controlled clinical trial including patients with scleroderma-associated Raynaud's phenomenon showed no clear evidence for the beneficial effect of BTx-A in the treatment of Raynaud's phenomenon.[14] In this study, 40 patients were enrolled and received 50 units of BTx injections in one randomly selected hand and sterile saline in the opposite hand. The primary outcome of the study, namely the change in blood flow from baseline to 1-month follow-up, showed a statistical decrease in blood flow of 36.19 flux units in treated hands as compared to 6.10 flux units in placebo hands. The change of blood flow was statistically not different from baseline to 4-month follow-up. The authors report that their subgroup analysis showed that the overall negative results of the study were mainly influenced by patients who had a longer time since Raynaud's phenomenon onset (>15 years) and those patients with diffuse scleroderma. According to the authors, it is also possible that the negative results were in part due to their screening methods for inclusion. The findings of the latter study are apparent as

one would expect a higher blood flow in treated hands, likewise the results of several other reports.[2,7] Neumeister et al[2] demonstrated an increase in perfusion in each digit within 30 minutes after injection with BTx in 10 (71%) out of 14 patients.

It is currently not exactly clear how BTx improves symptoms of vasospastic attacks and pain in patients with Raynaud's phenomenon. The action of BTx in Raynaud's phenomenon is not just by preventing the release of acetylcholine. BTx also inhibits noradrenalin release and reduces expression of alpha-2C adrenoreceptors. Very notable is the pain reduction that is instantaneous in some patients. This may be the result of inhibited exocytose of pain-mediating neurotransmitters such as substance P and glutamate.[2,5,13,15] The main reported side effect of BTx noted in studies is loss of muscle strength. In the study by Bello et al,[14] two out of 40 patients reported weakness of the muscles of the hand 7 days postinjection and fully recovered by 3 and 9 weeks.

Presently, it is unclear which properties determine the success of BTx injections in every individual. Smoking, prolonged and aggravated disease theoretically may have a negative impact on efficacy. The literature on these topics is however limited. Also, it is unknown whether the positive effects will be maintained after repeated injections. There is clearly a need for further research, in a randomized controlled trial, with stratification of patient groups. In addition, it would be highly interesting to also focus on blood flow evaluation in further studies.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Concerns a case series.

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