Case report

# The novel use of botulinum toxin A for the treatment of Raynaud's phenomenon in the toes

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Summary

raynaud's phenomenon is a vasospastic disorder of the digital vessels triggered by exposure to cold or stress.

It is most commonly observed in the hands, but also frequently affects the toes. We present three cases of patients with severe raynaud's phenomenon in the toes, secondary to scleroderma. the diagnosis of raynaud's syndrome and scleroderma was established according

to the 2010 american College of rheumatology and european League against rheumatism criteria. patients were treated with 10 units of botulinum toxin injected into each foot. two millilitres was injected into the

base of each toe in both the left and right feet. six weeks postinjection into the toes, patients reported an improvement of cold intolerance, colour change and frequency and severity of raynaud's attacks. the effects were reported to last up to 5 months. to our knowledge, these are the first reported cases of the treatment of raynaud's phenomenon in the toes with botulinum toxin a.

**Background**

Raynaud's phenomenon (RP) is a vasospastic disorder of the digital vessels triggered by exposure to cold or stress. It is most commonly observed in the hands but is also frequently occurs in toes.1 This transient digital ischaemia is classically character- ised by three phases: (1) ischaemia, (2) cyanosis and (3) reperfusion, with patient experiencing colour changes from white to blue to red.2 The prevalence of RP in the general population is between 3% and

5% and it is more common in women with a ratio of 4:1 (F:M).1 Patients often report severe pain, paraesthesia and swelling of the toes and feet.

Primary RP (Raynaud's disease) is idiopathic. Secondary RP (Raynaud's syndrome) has several causes and often occurs in the context of underlying autoimmune or connective tissue diseases. Sclero- derma is the most common cause; 90% of patients have RP. Other causes include Sjorgen's disease, rheumatoid arthritis, systemic lupus erythematosus (SLE), the contraceptive pill/oral contraceptives and β-blockers. These patients present later, with more severe disease and associated complications such as ulceration, gangrene and possible ampu- tation.1–3 It is an important therapeutic challenge.

The medical treatment options for RP depend on the underlying cause and severity. Patients with secondary RP are much more clinically challenging to treat as digital vasospasm can be aggravated by other disease manifestations. Botulinum toxin A

(Btx-A) is a neurotoxin produced by Clostridium botulinum.4 It has shown promise as a therapeutic option for patients with severe RP in the fingers that is refractory to other treatments.2 3 However, overall evidence conflicting and further randomised controlled trials (RCTs) are needed if Btx-A is to become a viable treatment option.5 Furthermore, there are currently no studies in the literature that report the use of Btx-A for the treatment of RP in the toes.

**Case Presentation**

Three patients with RP secondary to scleroderma, according to the criteria for systemic sclerosis of the American College of Rheumatology and European League Against Rheumatism criteria, presented to clinic. They all had moderate to severe scleroderma with severe RP that was refractory to previous medical treatment. No other concurrent treatments were changed or interrupted. See table 1 for full patient drug history. All patients were women and aged between 42 and 64 years. In addition to hand symptoms, they also reported moderate to severe pain, swelling and colour changes in the toes. The first toe was most frequently and most severely affected.

**Treatment**

The patients were treated with 10 units of Btx-A (Botox; Allergan, Marlow, UK) reconstituted in 2 mL of saline, per foot. Two units were injected into each toe, around the neurovascular bundles, of both the left and right feet. All injections were performed by the senior author PEMB. Thermo- graphic images of the feet were taken pre-Btx-A injection (figure 1A) and 6 weeks post-Btx-A injection (figure 1B). Thermographic imaging was carried out after a period of 20 min acclimatisation in a temperature controlled room at (23±0.5°C). Patients wore their own clothes but were asked to remove shoes and socks. The patients were also asked to complete a daily Raynaud's attack diary for 6 weeks. After 6 weeks, they returned to clinic for a follow-up assessment.

**Outcome and Follow-up**

Six weeks postinjection, all three of the patients reported a large improvement in pain, colour changes and cold intolerance. All three had an increase in temperature 6 weeks postinjection. Two of the patients also reported a reduction in the frequency and severity of Raynaud's attacks with a quicker

novel treatment (new drug/intervention; established drug/procedure in new situation)

**Table 1 Patient drug history**

| patient number | raynaud's medications | other |
|---|---|---|
| 1 | Losartan | Nil |
| 2 | Losartan<br>Nifedipine | Thyroxine |
| 3 | Nil currently<br>Had previously tried losartan, nifedipine and iloprost infusions | Fluoxetine |

recovery when attacks occurred. The other patient reported a reduction in swelling of the feet. She previously had to wear two differently sized shoes due to foot swelling. Six weeks postinjection, she reported the swelling had reduced shoe size in one foot reduced by half a size. Thermographic imaging showed an increase in the temperature of the toes 6 weeks post injection (figure 1B) compared with pre-Btx-A treatment (figure 1A).

A retrospective telephone questionnaire found that the duration of effects were variable and ranged between 7 weeks and 5 months. All of the patients would have further Btx-A injection into the toes and would also recommend it to other patients.

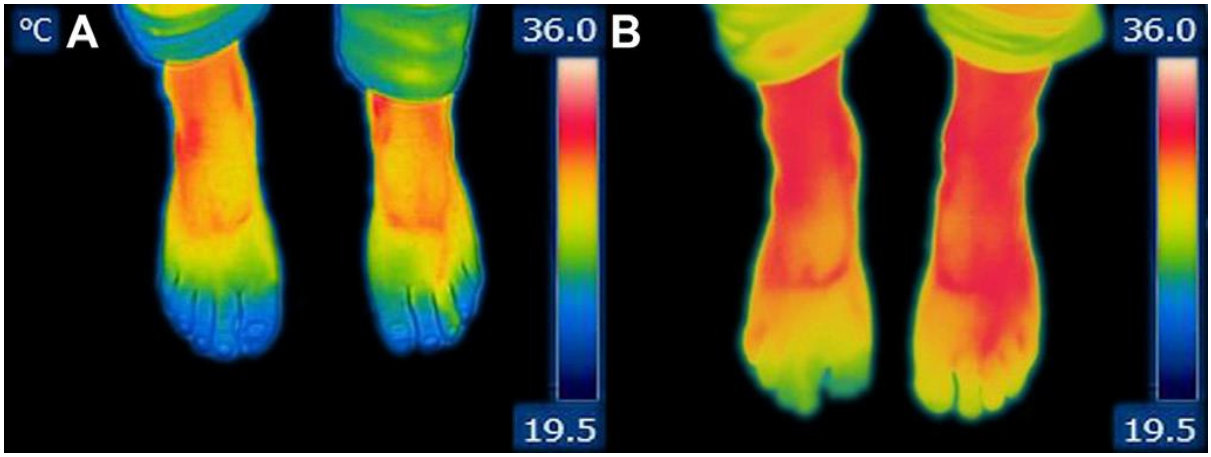
**Discussion**

The treatment options for severe RP that is refractory to medical treatment are very limited. Where medical management fails, surgical interventions are usually the next step. Current surgical options, such as digital sympathectomy, have the potential for severe complications with limited success.6 7 A systematic review found that of those patients having digital sympathectomy, 40% of patients have postoperative complications, 20% have continued ulceration and 15% go on to have amputations.8 The outcomes of digital sympathectomy of the toes is poorly reported in the liter- ature. There is currently only one case report that shows varying degrees of success in symptom improvement and ulcer healing in patients with scleroderma.9 10 Botulinum toxin offers an addi- tional, non-operative, treatment option for these patients. It is also unique in that it provides a localised treatment option, limiting the systemic side effects. All of the studies in the literature report its use in patients with finger symptoms. However, the majority of these patients also experience the same symptoms in the toes. There are currently no local treatments for toe symptoms.

We found that the temperature of the toes improved after Btx-A injection. It is known that Btx-A acts by inhibiting the release of acetylcholine release at the neuromuscular junction by binding to the SNAP-25 protein.2 However, the known mechanism

of action is unable to account for the results seen when it is used in the treat- ment of RP. Although this mechanism of action is currently not fully understood, it is thought that Btx-A causes vasodilation via

**figure 1** Patient 1 (A) Pre-Btx-A injection, (B) 6 weeks post-Btx-A injection. Btx-A,botulinum toxin A.




the inhibition of sympathetic neuronal transmission. Blocking the release of norepinephrine and other vasoconstrictive substances causes vasodilation at the neuromuscular junction of smooth muscle. This results in an increased blood supply to the digits.11

This is supported by a recent study that found an increase in the viability of skin flaps after Btx-A injection.12

From this case report, we found that Btx-A improved symptoms in patients with RP affecting the toes that is refractory to medical management. The Btx-A was well tolerated and results were promising. Further, larger controlled trial are needed to further investi- gate the role of Btx-A in treatment of RP in the toes.

**learning points**

► Raynaud's phenomenon (RP) is a vasospastic disorder of the digital vessels triggered by exposure to cold or stress.

► It is most commonly observed in the hands, but also frequently affects the toes.

► Botulinum toxin A (Btx-A) is a potential treatment option in those patients with severe RP in the fingers that is refractory to other treatment, however further RCTs are needed if Btx-A is to become a viable treatment option.

► On the basis of our case report, Btx-A has been shown to improve symptoms in patients with RP affecting the toes that is refractory to medical management.

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