

Botulinum toxin in the treatment of Raynaud phenomenon in patients with systemic sclerosis: a systemic review

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To the Editor: Raynaud phenomenon (RP) is a transient, vasospastic phenomenon that is prominent in systemic sclerosis (SSc). Most patients with SSc develop RP and can result in recurrent digital ulcers (DU) and critical ischemic events. General management of RP, including lifestyle changes, pharmacological and surgical intervention, can hardly lead to optimal remission of RP symptoms and ischemic complications quickly.

Botulinum toxin (BTX) injection has been investigated as a treatment option in RP. In 2004, two RP patients were successfully treated with BTX-A for the first time. In recent years, clinical trials have been carried out to assess the therapeutic efficacy of local injections with BTX in improving primary and secondary RP.^[1] However, the efficacy, best injection protocol, and side effects of BTX in treating RP secondary to SSc (SSc-RP) need to be systemically reviewed. Here, we analyzed the published clinical studies relevant to the therapeutic effect of BTX in treating SSc-RP, aiming to renew our recognition of the treatment.

This systemic review has been registered on PROSPERO (International Prospective Register of Systematic Reviews, ID: CRD42020158574). We utilized a string made up of relevant keywords (“scleroderma” or “systemic sclerosis” or “SSc”) AND (“botulinum toxin” or “clostridium botulinum toxins” or “botulin”) [Supplementary Table 1, <http://links.lww.com/CM9/A860>]. A literature search was conducted using PubMed, Cochrane Library, Embase, and Web of Science in January 2021 for all articles published from 1995 to 2021.

The initial search yielded 251 articles, which were narrowed down to five according to the inclusion and exclusion criteria [Supplementary Table 2, <http://links.lww.com/CM9/A860>]. The study selection process is shown in [Supplementary Figure 1, <http://links.lww.com/CM9/A860>]. We had gotten three case series

studies^[2-4] and two randomized controlled trials (RCTs)^[5,6] finally. The risk of bias of the included studies is illustrated in [Supplementary Figure 2, <http://links.lww.com/CM9/A860>].

A total of five articles involving 155 patients were assessed in this systemic review. 10.3% (16/155) of the enrolled patients were males, and 89.7% (139/155) were females. Patient characteristics are listed in [Supplementary Table 3, <http://links.lww.com/CM9/A860>]. All patients included in this study suffered from severe symptoms of SSc-RP and had failed conventional medical treatment or surgical therapy.

A variety of protocols for BTX injection were used. The studies differed with respect to doses and sites of BTX injection as well as the type of BTX [Supplementary Table 3, <http://links.lww.com/CM9/A860>]. Four studies used BTX-A^[2-5] while one RCT done by Motegi *et al*^[2] used BTX-B for injection.^[6] The dose of BTX-A varied from 10 U to 100 U,^[3-5] and the dose of BTX-B included 250 U, 1000 U, and 2000 U.^[6] In three studies, BTX was injected into the palmar aspect of the hand, targeting the neurovascular bundles^[2,3,6] and in two studies, BTX was injected into the dorsal surface near the proximal phalanx base.^[4,5]

The researches support the efficacy of local BTX injection for the treatment of SSc-RP. Most of the studies (four studies including 115 patients) showed that BTX injection was effective in the treatment of RP and related DUs in patients with SSc.^[2-4,6] It could improve the symptoms of SSc-RP, reduce the pain, and heal intractable DUs.

Motegi *et al*^[2] measured severity of RP, Raynaud score including frequency, pain, color, and duration, as the primary endpoint, and change in temperature after cold-water challenge, number of DUs, and pain Visual Analogue Scale (VAS) as the secondary endpoint in 45 and 10 patients, respectively (no overlap between two groups).^[6] They found that Raynaud score and pain VAS

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score in the BTX group was significantly lower than that in the control group ($P < 0.05$), and skin temperature recovery after cold-water stimulation was significantly improved after BTX injection. The numbers of DUs in the BTX group were also significantly lower in 4 to 16 weeks after injection.

Uppal *et al*^[3] assessed hand function, joint movement, ulcer healing, and subjective feeling including pain, color change, and cold intolerance in 20 patients. They found that hand function and the ranges of joint movement of the fingers were statistically significantly improved. Besides, 75% of the patients who had ulceration in fingers showed complete healing and 80% of the patients showed improvement in symptoms of the injected hands.

However, Bello *et al*^[5] reported a negative result showing that although the enrolled 40 patients had slightly better outcomes after injecting BTX-A into affected hands, the difference was not statistically significant. They performed a subgroup analysis according to SSc subtype, RP disease duration, RP severity, and baseline treatment, and found that patients with longer disease duration since RP onset (>15.56 years) and diffuse scleroderma subtype might respond worse to BTX injection.^[5]

We further focused on the influence of BTX type (BTX-A and BTX-B) on the efficacy of SSc-RP. In the included studies, four studies including 110 patients used BTX-A,^[2,3,5] one study including 45 patients used BTX-B.^[6] Among the four studies using BTX-A, three case series studies showed great efficacy,^[2-4] and one RCT showed the differences were not statistically significant.^[5]

Both BTX-A and BTX-B can produce good efficacy although the optimal doses were different. BTX-B was effective at approximately 20 to 40 times the dose of BTX-A in the treatment of SSc-RP according to Motegi *et al*.^[6] The doses of as low as 10 U to 100 U BTX-A have been reported to show favorable results.^[2-4] We did not find the difference in treatment effects among different dosages. As for the injection dose of BTX-B, Motegi *et al*^[6] found that the effective dose might be ≥ 1000 U, and both 1000 U and 2000 U had similar treatment effects while the 2000 U group might improve skin surface temperature better.^[6]

The studies reported different onset times of pain reduction and times of ulcer healing. The onset time of pain reduction varied from as soon as 2 weeks to within 16 weeks after injection. The healing time of DUs was 12 weeks. The duration of efficacy was between 4 and 6 months.

The injection sites were described differently, but most of the studies injected BTX around the neurovascular bundles proximal to the A1 pulley, the space next to the metacarpophalangeal joint. Motegi *et al*^[6] and Uppal *et al*^[3] injected BTX into the palmar aspect of the hand,

while Bello *et al*^[5] who got the negative result injected BTX into the dorsal surface of the hand. It seems that the palmar aspect might be a better injection site.

The major finding of this systemic review is that researches support the efficacy and safety of local BTX injection for the treatment of SSc-RP. The injection site getting close to the sclerosis lesions, near the digital neurovascular, might be suitable. The dose of as low as 10 U and up to 100 U of BTX-A, and 1000 U or 2000 U BTX-B could all produce great efficacy, while the higher dose may lead to more side effects. Larger double-blind, prospective, randomized, placebo-controlled studies are needed to confirm the beneficial efficacy of BTX on the treatment of SSc-RP, determine injection protocol, and explore different subgroups of patients responding to BTX injection, hence providing high-quality evidence to support future clinical decision-making.

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Conflicts of interest

None.

References

- Ennis D, Ahmad Z, Anderson MA, Johnson SR. Botulinum toxin in the management of primary and secondary Raynaud's phenomenon. *Best Pract Res Clin Rheumatol* 2021;35:101684. doi: 10.1016/j.berh.2021.101684.
- Motegi S, Yamada K, Toki S, Uchiyama A, Kubota Y, Nakamura T, *et al*. Beneficial effect of botulinum toxin A on Raynaud's phenomenon in Japanese patients with systemic sclerosis: a prospective, case series study. *J Dermatol* 2016;43:56–62. doi: 10.1111/1346-8138.13030.
- Uppal L, Dhaliwal K, Butler PE. A prospective study of the use of botulinum toxin injections in the treatment of Raynaud's syndrome associated with scleroderma. *J Hand Surg Eur Vol* 2014;39:876–880. doi: 10.1177/1753193413516242.
- Dhaliwal K, Griffin MF, Salinas S, Howell K, Denton CP, Butler PEM. Optimisation of botulinum toxin type a treatment for the management of Raynaud's phenomenon using a dorsal approach: a prospective case series. *Clin Rheumatol* 2019;38:3669–3676. doi: 10.1007/s10067-019-04762-4.
- Bello RJ, Cooney CM, Melamed E, Follmar K, Yenokyan G, Leatherman G, *et al*. The therapeutic efficacy of botulinum toxin in treating scleroderma-associated Raynaud's phenomenon: a Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *Arthritis Rheumatol* 2017;69:1661–1669. doi: 10.1002/art.40123.
- Motegi SI, Uehara A, Yamada K, Sekiguchi A, Fujiwara C, Toki S, *et al*. Efficacy of botulinum toxin B injection for Raynaud's phenomenon and digital ulcers in patients with systemic sclerosis. *Acta Derm Venereol* 2017;97:843–850. doi: 10.2340/00015555-2665.

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