

Botulinum toxin for Raynaud's phenomenon: an usefull but seldom reminded therapy for severe cases

Toxina botulínica e Fenômeno de Raynaud: terapia útil mas pouco lembrada para casos severos

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ABSTRACT

Introduction: Raynaud's phenomenon (RP) is an exaggerated physiological response of the extremity vessels, mainly to cold and stress. Patients refractory to clinical treatment or intolerant to its adverse events may be treated with local injection of botulinum toxin (BTX).

Objective: To describe the experience of botulinum toxin use in severe cases of RP.

Methods: Observational, descriptive, retrospective, and unicenter study of case series of severe RP treated with BTX-A, from 2011 to 2015. Parameters of pain, numbness, color, and stiffness were scored by visual analogical scale (VAS) and tabulated and compared before and after the treatment.

Results: Total pain improvement in 71.4% of cases and partial improvement in 28.6%. Numbness disappeared in 57.1% of cases and improvement in 42.9%. There was a total regression of stiffness in 57.1% of cases and partial improvement in 28.6%. The color was completely reversed in 57.1% of the patients. There was ulceration healing in the only case in which they were present. Ischemic attacks were reduced in 85.7% of cases. No complications occurred.

Conclusions: This study suggests that the use of BTX-A in patients with severe RP is a promising therapeutic option.

Keywords: Raynaud disease; Botulinum toxins; Botulinum toxins, type A

RESUMO

Introdução: O fenômeno de Raynaud (FR) é uma resposta fisiológica exagerada dos vasos das extremidades, principalmente ao frio e ao estresse. Pacientes refratários ao tratamento clínico ou intolerantes aos seus efeitos colaterais podem ser tratados com injeção local de toxina botulínica.

Objetivo: Descrever a experiência do uso da toxina botulínica em casos severos de FR.

Métodos: Estudo observacional, descritivo, retrospectivo e unicêntrico de série de casos de FR graves tratados com toxina botulínica-A, no período de 2011 a 2015. Parâmetros de dor, dormência, cor e rigidez foram pontuados por escala visual analógica e comparados antes e depois do tratamento.

Resultados: Melhora total da dor em 71,4% dos casos e parcial em 28,6%. A dormência desapareceu em 57,1% dos casos e melhorou em 42,9%. Houve regressão total da rigidez em 57,1% dos casos e melhora parcial em 28,6%. A cor foi completamente revertida em 57,1% dos pacientes. Houve cicatrização das ulcerações no único caso em que estavam presentes. Houve redução dos ataques isquêmicos em 85,7% dos casos. Não ocorreram complicações.

Conclusões: Este estudo sugere que o uso da toxina botulínica A em pacientes com fenômeno de Raynaud grave é opção terapêutica promissora.

Palavras-Chave: Doença de Raynaud; Toxinas botulínicas; Toxinas botulínicas tipo A

Original Article

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INTRODUCTION

Raynaud's phenomenon (RP) is an exaggerated physiological response of the extremity vessels, especially to cold and emotional stress.¹ Traditionally, three phases characterizes it: pallor (vasoconstriction), cyanosis (due to blood deoxygenation), and redness (reactive hyperemia).²

Most cases of RP are classified as primary or idiopathic and are not associated with other conditions. Less often, RP is classified as secondary and is associated with conditions such as connective tissue diseases, especially systemic scleroderma (SSc).^{3,4}

The pathogenesis of primary RP is related to the exacerbated stimulation of alpha-adrenergic receptors present in vascular smooth muscle, causing its vasoconstriction. Primary RP can be controlled with preventive measures, keeping the patient away from triggering factors such as cold exposure, stress, caffeine, vasoconstrictor medications, and smoking.^{1,4} On the other hand, in secondary RP, the presence of structural vasculopathies characteristic of associated diseases potentiates the reduction of vessel caliber and makes such patients more prone to develop pain, numbness, and ischemic complications, such as functional limitation, digital ulcers, and partial digit amputations, promoting strong impact on quality of life.⁴

In the presence of RP signs and symptoms, despite the adoption of preventive measures, pharmacological treatment is required to regulate vasodilation/ vasoconstriction. Several drug classes are available, such as antiplatelet agents, cilostazol, sarpogrelate, intravenous and oral prostanoids, phosphodiesterase type 5 inhibitors (PDE5), endothelin receptor antagonists (ERA), and bosentan. However, calcium channel blockers remain the therapy of choice in treating this condition.⁵ When patients are refractory to clinical treatment or cannot tolerate the adverse events, there are few alternative therapies, including surgical treatment (periarterial sympathectomy), and, more recently, the use of local botulinum toxin injection (BTX).⁶

Botulinum toxin is a polypeptide composed of a light chain (50kDa) and a heavy chain (100kDa) joined by disulfide bond. It is produced by the gram-negative bacterium *Clostridium botulinum* and was discovered in 1897 by Emile van Ermengen, in Belgium. In 1949, Arnold Burgen described the first elucidation of its mechanism of action as an inhibitor of acetylcholine release in neuromuscular junctions.⁷

Of the seven existing types of BTX (A-G), two (BTX-A and BTX-B) have been successfully used in both dermatological and cosmetic therapy, and in recent years they have been cited as a therapeutic option for symptomatic RP cases refractory to clinical treatment. This is because they act on the various pathogenesis of the disease, inhibiting adrenergic or cholinergic sympathetic vasoconstriction and acting on various pain-related neurotransmitters, such as norepinephrine, substance P, glutamate, and calcitonin gene-related peptide (CGRP).^{2,8-11}

Such use was first reported in 2004 by Sycha *et al.* in two patients with severe and intractable Raynaud's phenomenon. These patients showed improvement in stiffness and numbness as well as increased digital perfusion.¹²

In 2007, Vanbeek *et al.* described a series of 11 patients with Raynaud's phenomenon secondary to connective tissue di-

sease. In this study, the injections were performed only on the affected fingers, with early recurrence on the uninjected fingers, which justified a change in the treatment protocol for all fingers. All patients received a total dose of 100 U/hand and showed pain relief within two days (pain score decrease from 9-10 to 0-2). Nine out of 11 patients had ulcer healing and two underwent successful grafts.³

Then, Fregene *et al.* sought to standardize the injection technique in a series of 26 patients. However, statistical evaluation did not define a specific injection site with superior results.¹

Most botulinum toxin publications in RP show the experiences of countries in North America (USA and Canada), Europe (France, Austria and England), Asia (Japan and China), and South America (represented by Colombia only). However, so far, national research on the subject has not been found.

OBJECTIVE

To describe the experience of using botulinum toxin type A in patients with severe Raynaud's phenomenon.

METHODS

Observational, descriptive, retrospective, single-center, case series study conducted following the ethical principles of the Declaration of Helsinki, the Americas document, following the guidelines of Good Clinical Practice (GCP) and local laws of Brazil where it was developed. It was submitted and approved by the institution's Research Ethics Committee (REC) under number 3.510.407.

Patients older than 18 years of age, treated at the Collagenosis Outpatient Clinic of the Dermatological Clinic of the Hospital do Servidor Público Municipal de São Paulo (HSPM), from June 2011 to July 2015, were selected. The inclusion criteria were previous diagnosis of clinically evident RP refractory to clinical treatment; application of botulinum toxin to treat RP in the period mentioned; follow-up for at least four months after the application, and signature of the Informed Consent Form (ICF).

Patient data such as gender, age, associated disease and respective treatments, type of toxin, dose and mode of application, as well as the treated hand were evaluated. Information on pain, numbness, color, and stiffness were scored and evaluated using the visual analog scale (VAS) applied before and after the treatment. Episodes numbers, ulceration regression, follow-up time, and BTX adverse events were also recorded. All information was collected from the HSPM medical records and transcribed into a data collection table designed by the researchers.

RESULTS

We found seven women (100%) with a mean age of 45 years, ranging from 31 to 56 years. All had been treated with BTX-A injections on the lateral and medial surfaces of the finger bases, as shown in Figure 1.

The doses applied were 10 UI/finger in one case (14.3%) and 5 UI/finger in six cases (85.7%). All seven patients had RP

secondary to collagenosis (100%), one had dermatomyositis (14.3%), one had systemic lupus erythematosus (14.3%), two had systemic sclerosis (28.55%), two had mixed connective tissue disease (28.55%), and one had Sjögren's syndrome (14.3%). Table 1 presents the demographic data.

The mean follow-up was 11.4 months, ranging from 4 to 18 months. Pain improved by 100% in five of the seven cases (71.4%). In the remaining two cases (28.6%), this improvement was over 70%. Numbness disappeared after treatment in four of seven cases (57.1%) and improved 70% or more in three cases (42.9%). Regarding finger stiffness, there was total regression in four of seven patients (57.1%), partial improvement greater than 50% in two cases (28.6%), and no change in one patient (14.3%). The color, which was related to perfusion, was reversed entirely from purple to normal in four of seven cases (57.1%), and in three cases (42.9%), there was no change.

In the only case where ulcerations were present, complete healing occurred within 90 days post-toxin. Regarding the frequency of ischemic attacks, in six women (85.7%) the reduction ranged from 50% to 100%, and in only one case (14.3%) it did not change. No early or late postoperative complications were described in any of the seven patients.

DISCUSSION

Since the first description in 2004 by Sycha *et al.*, several authors have been reporting promising results in the use of botulinum toxin for refractory RP cases.^{1,3,5,8,11}

In our study, we used BTX-A to treat RP in 100% of patients, following the literature trend due to its already valida-

ted indications. Only one study used serotype B.^{2,13} According to Kranz *et al.*, in 2010 there would be no difference in efficacy between these serotypes, and only their pharmacokinetics would be different. BTX-A would have the advantage of presenting a longer duration of action (>1 year), reducing the frequency of injections.¹⁴

Several studies describe botulinum toxin use, but most use heterogeneous populations, including patients with primary RP (which by definition is not associated with an underlying connective tissue disease) or with RP secondary to other connective tissue diseases.^{1,3,4,7,8,12,15-17} Only five studies specifically focus on RP secondary to scleroderma,^{2,13,18-20} limiting the interpretation of the evidence for this patient population.¹⁹

In our study, we used a heterogeneous group of patients with RP secondary to five different types of collagenosis. Only one of these patients, who had more severe sclerosis, responded less well to treatment, as in a single case series suggesting that individuals with sclerosis may be less responsive to BTX-A injections compared to other patients with RP.⁸ This may be because in scleroderma there is an association of vasospasm with the sclerotic mechanical component of the arterial wall that could theoretically make this group more prone to severe symptoms, frequent ischemia, and complications, as well as reducing its response to toxin.^{4,21,22}

All other patients in our study, including the less severe case of scleroderma, presented a good response to BTX, suggesting that this treatment is also effective in RP secondary to scleroderma^{2,14,18-22} and the other collagenoses.^{1,3,4,12,17,18,23} Regarding toxin application, there is no consensus on dilutions, injection sites, and doses, which vary according to the authors.^{1-3,5} The doses used in our study follow the literature trend of 50U to 100U BTX-A per hand described by Van Beek and Neumeister.^{3,8}

Fregene *et al.* tried to standardize injection sites by separating patients into three application categories based on their symptoms: interdigital neurovascular bundles; distal superficial palmar arch; and proximal phalanges, adjacent to the radial and ulnar arteries in the wrist. However, the statistical evaluation was unable to find a better injection pattern.^{1,5}

Thus, as distal digital injections can be equally effective, there is currently a tendency to avoid toxin application in the palmar region, as it is associated with muscle weakness, even without statistical significance. This adverse event, found in the literature, is related to neuromodulator diffusion to the intrinsic hand musculature.^{1,2,5} In our study, injections were limited to the lateral and medial sides of the digits. Thus, we didn't observe muscle weakness in our cases.

A previous study reporting cases of early recurrence in non-treated fingers when injections were restricted to the affected fingers only justified the choice of applying the toxin to the base of all fingers (affected or not) in both hands.^{3,5}

Regarding the clinical presentation of RP, BTX-A injections showed promising results in improving pain, numbness, stiffness, number of seizures, ulcerations, and cold sensitivity.^{1,3,5,8,12}

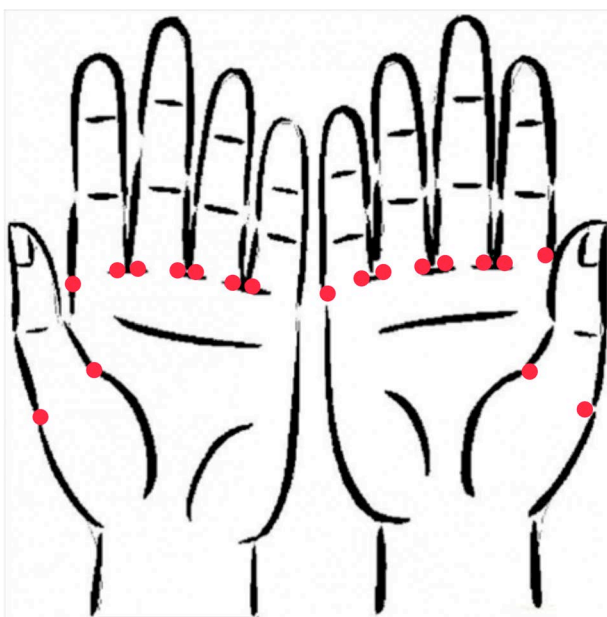


FIGURE 1: BTX-A Application Points

TABLE 1: CASE REPORT TABLE

Case	Sex/ Age (years)	Asso- ciated sys- temic disease	Botu- linum toxin used	BTX dose applied	BTX Applica- tion mode	Hand treat- ed	Pain (0-10 points)	Numb- ness(0-10 points)	N crises / week	Coloring(nor- mal)/ pale/ red/purple)	Stiff- ness(0-10 points)	Ulcers(Yes/ No)	Follow-up time	Complica- tions	Medication- sin use
1ABM	F 51	DM	BTX-A	5U/Finger 50u/Hand	Interdigital	Both	A 8	A 6	A Daily	A D Pur- ple	A 4	A N	18 months	Absent	MTX DC AAS- Nifedipine Cilostazol
2SMG	F 56	ES	BTX-A	5U/Finger 50u/Hand	Interdigital	Both	7 0	10 0	Daily 2	Pur- ple	4 4	N N	13 months	Absent	Colchicine Diltiazem Simvastatin
3ABS	F 50	SJ	BTX-A	5U/Finger 50u/Hand	Interdigital	Both	10 0	8 2	3x 1x	Pur- ple	7 0	N N	13 months	Absent	Prednisone MTX AINH
4LSS	F 32	DMTC	BTX-A	5U/Finger 50u/Hand	Interdigital	Both	5 9	10 3	Daily 3x	Pur- ple	2 0	N N	11 months	Absent	DC MTXPent- oxifyline
5LBLC	F 39	DMTC	BTX-A	5U/Finger 50u/Hand	Interdigital	Both	9 2	10 2	Daily 3x	Pur- ple	10 3	N N	10 months	Absent	Prednisone MTXPentoxi- fyline
6LGA	F 31	LES	BTX-A	5U/Finger 50u/Hand	Interdigital	Both	7 0	8 0	Daily 1x	Pur- ple	9 0	N N	11 months	Absent	HCQ AINH
7CPC	F 54	ES	BTX-A	10U/Fin- ger 100u/ Hand	Interdigital	Both	7 2	4 0	3x 3x	Pur- ple	9 4	S N	4 months	Absent	Bosentan Omeprazol Pentoxifilina Sildenafil

Scale: 0-10 symptoms; 10-0 m

Abbreviations: B - Before botulinum toxin; A - After botulinum toxin; Y - presence of ulcers; N - absence of ulcers; BTX- Botulinum toxin; DM- Dermatomyositis; MCTD - Mixed connective tissue disease; SC- Systemic scleroderma; F- Female; SLE- Systemic lupus erythematosus; MTX-Methotrexate; HCQ: Hydroxychloroquine; CD-Chloroquine diphosphate; ASA-Acetylsalicylic acid; nl: Normal

Decreased muscle contraction can explain the reduction of stiffness symptoms. When the toxin undergoes endocytosis in the presynaptic nerve ending, it binds to synaptosome nerve-associated protein 25 (SNAP-25 of the SNARE complex), inhibiting it and preventing the mobilization and exocytosis of acetylcholine vesicles in the nerve terminal membrane. Without cholinergic stimulation, muscle cells do not contract, contributing to the treatment of stiffness observed in patients.^{2,23,11} Our results showed improvement of this symptom, with total regression in 57.1% of patients, and partial regression in 28.6% of them, is consistent with the literature.^{2,11,12,17,23}

Cholinergic neuromuscular action can also explain pain and numbness reduction, since vascular smooth muscle cells are also inhibited, promoting vasodilation and reperfusion. However, some authors question whether there would be other mechanisms involved. This is because the effect of the toxin on pain and numbness modulation is immediate and could not be explained only by the anticholinergic action, which would require a longer time to cause muscle paralysis and, consequently, flow restoration. BTX-A also acts by blocking several neurotransmitters related to C-fiber depolarization that propagate chronic pain, such as norepinephrine, substance P, glutamate, and calcitonin gene-related peptide.^{2,11,23}

Another possible mechanism of action is the inhibition of alpha-2 adrenergic receptor expression both in the peripheral nerve walls chronically irritated by ischemia or trauma and in the vessel walls, suppressing cold-induced noradrenergic vasoconstriction. Also, it has been reported that, *in vitro*, the toxin would reduce the intracellular accumulation of reactive oxygen species (ROS) produced in response to cooling, which is responsible for enhancing surface expression of adrenergic receptors. Finally, BTX-A could further reduce pain by inhibiting ectopic sodium channels expressed chronically in nerves irritated or injured by chronic ischemia in patients with RP.²⁰

Two case series reported pain and numbness improvement with the use of BTX-A was reported, which described a decrease in both symptoms in all patients evaluated.^{12,18} Other

16 studies have shown pain reduction in 75% to 100% of cases, but with no evaluation of numbness.^{1-3,6-8,11,13,16,18-21,23-25} In our study, total pain regression occurred in 71.4% of cases and partial improvement in the remaining 28.6%. Numbness disappeared in 57.1% of patients and partially decreased in 42.9%.

The normalization of the finger color using BTX-A is also described by some authors.^{1,11,20,24} The vasodilation provided by the neuromodulator leads to the blood flow restoration and fingers reperfusion. Thus, the fingers resume their pink color. In our study, 57.1% of the patients had a complete change from purple to pink, as shown in Figure 2.

A similar mechanism of action justifies the beneficial effects of BTX-A on the healing of digital ulcers secondary to RP.⁵ By acting to prevent dysregulation between vasoconstriction and vasodilation in RP, the toxin disrupts the vicious cycle of ischemia-reperfusion (I/R). Blood reperfusion would lead to infiltration of inflammatory cells and production of pro-inflammatory cytokines in previously ischemic tissue, resulting in damage to vascular endothelium, edema, capillary narrowing, apoptosis, and tissue necrosis.^{20,26,27}

An experimental study showed that BTX-A injection prevented the formation of skin ulcers after I/R induction in a murine model. The toxin reduced the area of hypoxic tissue and protected it from oxidative stress and cell apoptosis.²⁸ Another 10 publications have reported human cases of healing of digital ulcer secondary to RP with BTX-A.^{2,3,8,13,16-21,23,25} In the only case of our study where ulcers were present, there was complete lesion closure within 90 days post-toxin (Figure 3), following the findings in the literature.

Regarding the frequency of ischemic attacks, our results showed a reduction in the number of episodes and were similar to those found in three other studies.^{3,18,20} Although the mechanism of action is not well established, it is believed that the toxin would act by reducing the expression of alpha-2-adrenergic receptors on vessel surfaces. Thus, patients would become less responsive to sympathetic discharges triggered by cold and stress,⁷ stimuli considered the main provokers of vasoconstriction and ischemic attacks in RP.¹

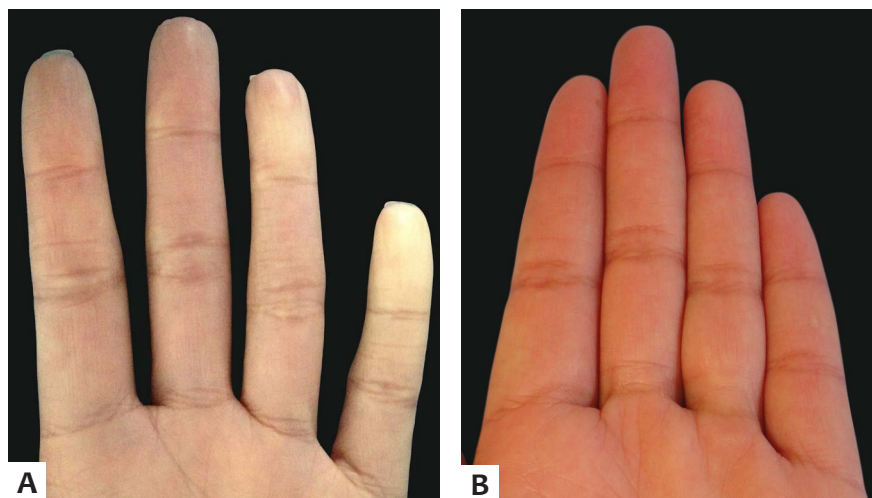


FIGURE 2:

A: RP ischemic phase in the 4th and 5th fingers of the left hand. **B:** Improved finger color



FIGURE 3: Ulceration healing 3 months after BTX-A injection

CONCLUSION

Further research is still needed to build consensus on BTX-A doses, dilutions, and injection sites. Despite the small sample size, the beneficial and fast toxin results seen in our case

series suggest this medication may be a promising therapeutic option in refractory RP cases.

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