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Is Botulinum Toxin Effective at Reducing Sensory Symptoms in the Hands of Patients with Raynaud's Phenomenon?

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Is Botulinum Toxin Effective at Reducing Sensory Symptoms in the Hands of Patients with Raynaud's Phenomenon?

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ABSTRACT

Objective: The objective of this systematic review is to determine, "Is Botulinum Toxin Effective at Reducing Sensory Symptoms in the Hands of Patients with Raynaud's Phenomenon?"

Study Design: A systematic review of two randomized controlled trials (RCTs) and one prospective case series published between 2017 and 2019.

Data Sources: The articles were discovered using PubMed or Academic Search Premier. The articles were published in English in peer-reviewed journals and selected based on pertinence to the clinical question.

Outcome Measured: A reduction in sensory symptoms was the outcome measured in all three studies using the VAS pain score (0-10/100) or McCabe Cold Sensitivity Score (0-400).

Results: In the prospective case series led by Dhaliwal, VAS pain score decreased after post-Btx-A treatment at 12-weeks, indicated by a mean change from baseline of 2 ($p = 0.05$). In the RCT led by Bello, McCabe Cold Sensitivity Score decreased 39.6 points in the Btx-A group after 4 months ($p = 0.906$). Additionally, VAS pain score reduced 1.44 points in the Btx-A group after 4 months ($p = 0.327$). In the RCT led by Motegi, VAS pain score decreased in the Btx-B group by 12 weeks, indicated by a mean change from baseline of 50% ($p < 0.05$).

Conclusion: Dhaliwal et al. and Motegi et al. provide statistically significant evidence that botulinum toxin reduces sensory symptoms in patients with RP, however, Bello et al. does not support this hypothesis. It cannot be determined whether botulinum toxin improves sensory symptoms in patients with RP.

Key Words: Raynauds, botox

INTRODUCTION

Raynaud's phenomenon (RP) is a sudden, exaggerated spasm of the digital arterioles to cold temperatures or emotional stress. A true diagnosis of RP includes color changes of the hands or feet (sometimes even the ears or nose), in addition to discomfort or extreme pain. There are two types of RP, primary, also known as Raynauds disease, or secondary. Both types of RP mainly affect women compared to men. Primary RP is idiopathic and typically presents between the ages 15 and 30. Secondary RP predominantly develops in patients with another illness, most commonly being connective tissue diseases like systemic sclerosis (scleroderma) or lupus. This type of RP tends to occur in patients over the age of 30 and is generally more severe, leading to complications including ulcers and gangrene.[1] Up to 5% of the general population has Raynaud's.[2] The total healthcare cost of RP is unknown, but the first-line pharmacologic treatment for RP is nifedipine, a calcium channel blocker that can range from $75-200 per month.[3] Additionally, for severe cases, PDE5 inhibitors like sildenafil can be used, costing about $826 per month.[3,4] The exact number of healthcare visits for RP each year is unclear, however, high volume of physician services is used for secondary RP, involving patients with systemic sclerosis, Sjogren's syndrome, rheumatoid arthritis, or lupus.[5]

The underlying cause of RP is still under investigation, however, it is a vasospasm of the digits in response to cold temperatures, stress, or other physical or medical exposures.[3] The initial color change is white or pallor due to vasoconstriction, then it changes to blue or cyanotic due to deoxygenation, and lastly red because of vasodilation/reperfusion. Primary RP tends to be more symmetric, episodic, and without evidence of peripheral vascular disease. Secondary RP is more frequent, painful, asymmetric, and can lead to digital ulcerations.[3] Treatment for RP depends on its severity. Less severe symptoms may be treated with diet and lifestyle

modifications. Avoidance of cold stimuli, tobacco, and sympathomimetics, as well as reducing stress, exercising more, and wearing mittens and hats, are some non-pharmacologic options. Pharmacotherapy can be utilized for more symptomatic RP, and these medications include calcium channel blockers, angiotensin II receptor blockers, topical nitrates, phosphodiesterase inhibitors, SSRIs, statins, endothelin-receptor inhibitors, and IV prostacyclin or prostacyclin analogs. Refractory or severe cases like digital ischemia and ulcers are indications for surgery, with a procedure called digital artery sympathectomy.[2]

Calcium channel blockers (CCBs) work by causing vasodilation, thus reducing vasospasm in the arterioles. CCBs are confirmed to reduce the frequency, duration, severity of attacks, pain and disability associated with RP, however, nifedipine can have adverse side effects, including headache, flushing, constipation, fatigue, and peripheral edema.[4] Nifedipine, along with other pharmacologic agents may fail to improve symptoms in those with secondary RP, and thus surgery serves as a last-line therapy for these patients. A new, non-invasive alternative for unmanageable RP is botulinum toxin injection. Proposed mechanisms of botulinum toxin include inhibition of sympathetic adrenergic or cholinergic vasoconstriction and inhibition of sensory nerves, thus providing symptomatic relief.[6] This paper evaluates two randomized control trials (RCTs) and one prospective case series, assessing the efficacy of botulinum toxin as a treatment for Raynaud's phenomenon.

OBJECTIVE

The objective of this selective EBM review is to determine, "Is Botulinum Toxin Effective at Reducing Sensory Symptoms in the Hands of Patients with Raynaud's Phenomenon?"

METHODS

Studies were selected based on validity, pertinence to the clinical question regarding botulinum toxin as a treatment for RP, and incorporation of patient-oriented outcomes, specifically sensory symptoms. Inclusion criteria was articles of English language published in 2010 or later. Exclusion criteria was articles published before 2010, non-English language, and systematic reviews. The articles were discovered via PubMed and Academic Search Premier using the words “Raynauds” and “botox”.

The population targeted for this review was individuals with Raynauds phenomenon. The demographics and characteristics of these studies is included in Table 1. The intervention being investigated for sensory symptom reduction for RP is botulinum toxin A or B hand injection. Bello et al. used between-arm control and Botox A injection groups. Dhaliwal et al. compared pre- and post-Botox A injections at 12 weeks. Lastly, Motegi compared Botox B injections with a control group of no treatment. The outcomes measured were pain and cold sensitivity using VAS pain score and McCabe Cold Sensitivity Score, respectively. A summary of statistics reported includes p-values and mean change from baseline. The studies involved in this EBM review include a double-blind RCT, single-blind RCT, and prospective case series.

OUTCOME MEASURED

All three studies utilized the VAS (visual analog scale) pain score, a 0-100 mm or 0-10 cm scale that subjectively measures acute and chronic pain (0 = no pain, 100/10 = worst pain).[5,6,7] In addition to VAS score, Bello et al. utilized the McCabe Cold Sensitivity Score (0-400) to measure cold sensitivity in the hands of patients with RP.[6]

Table 1. Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Dhaliwal[5] (2019)	Prospective case series	40	25-76	Female patients were chosen with RP secondary to systemic sclerosis, a diagnosis criteria met by the ACR. None of the patients were smokers.	Active infections, acute digital ischemia, allergies to botox, pregnant or lactating.	0	Pre-BTX-A 100 inj. vs 12-week post inj.
Bello[6] (2017)	RCT	40	21-75	Patients with bilateral RP and scleroderma diagnosis criteria met by the ACR. Patients also have at least 3 of 5 features of CREST syndrome, or had definite RP, abnormal nailfold capillaries, and a scleroderma-specific autoantibody.	Active hand infection in either hand, acute digital ischemia, myasthenia gravis, allergies to botox, previously received botox, previous upper extremity vascular surgery, receiving aminoglycoside antibiotics, or pregnant or lactating.	0	BTX-A 50 U experimental hand vs. 2.5 ml sterile saline control hand
Motegi[7] (2017)	RCT	9	55-65	Patients with RP secondary to systemic sclerosis met by the American College of Rheumatology (ACR). Patients all have a history of severe RP and have taken oral prostanoids, beraprost sodium, and/or antiplatelet agents.	Patients under 18 years old, pregnant, and previously treated with BTX-B.	Not addressed.	BTX-B 250 U group vs. no treatment control

RESULTS

Dhaliwal et al. conducted a prospective case series on 40 female patients with RP secondary to scleroderma at the Royal Free Hospital between March 2015 and February 2016. Inclusion and exclusion criteria for selection of these patients can be found in Table 1. Of these 40 patients, 20 had diffuse scleroderma and 20 had limited scleroderma, with an average duration of disease of 15 years. Patient consent was obtained, and medications were continued throughout the study, including calcium channel blockers, iloprost, fluoxetine, PDE-5 inhibitors, and losartan. All patients were treated with 100 units of Btx-A, reconstituted with 2 ml of normal saline, across both hands in a dorsal fashion around the digital neurovascular bundles of all five digits. VAS pain scores (0-10 cm) in Pre-Btx-A and 12-week Post-Btx-A were compared. There were no adverse effects noted throughout the 12 weeks, other than injection site pain lasting 4 days in one patient and itching for the first 2 days in another patient. All participants were accounted for and attributed at its conclusion.[5]

As noted in Table 2, VAS pain score in pre-Btx-A was 5 and in 12-week post-Btx-A was 3, resulting in a mean change from baseline of 2 ($p = 0.05$). A p-value < 0.05 indicates statistical significance.[5]

Table 2. VAS Pain Score from Baseline to 12 Weeks Post Injection

	Baseline	12 weeks	Mean Change from Baseline	P-value
VAS Score	5	3	2	0.05

Bello et al. selected 40 patients to participate in a randomized, double-blind, parallel-group, placebo-controlled clinical trial at the Johns Hopkins Scleroderma Center in Baltimore, MD, between January and September 2015. All patients had a diagnosis of scleroderma in

addition to RP, with at least 3 of the 5 features of CREST syndrome according to the American College of Rheumatology. Twenty-five of these patients had limited scleroderma and 15 had diffuse scleroderma, with a median time of diagnosis of 14 years and median time since RP onset of 15.6 years. Thirty-one patients were women and 9 were men, with a mean age of 51.9 ± 12.3 years. Most patients were treating RP with calcium-channel blockers at baseline. Patients were selected based on specific inclusion and exclusion criteria listed in Table 1. Participants received dorsal injections (similar method as Dhaliwal et al.) of 50 units of Btx-A, reconstituted in 2.5 ml of sterile saline, in one randomly selected hand, and 2.5 ml of sterile saline in the opposite control hand. The study pharmacists created a random sequence with blocks of 4 patients to establish a treatment group allocation of 1:1 ratio, using Microsoft Excel 2007. Study participants and all study team members, except for the study pharmacists, were blinded to treatment allocation and size of randomization blocks. In-person study visits took place at 4 months post injection. VAS pain score (0-10 cm) and McCabe Cold Sensitivity Score were reported for each hand of every patient. All subjects who entered the trial were accounted for and attributed at its conclusion. Two participants (5%) experienced weakness of the intrinsic muscles of the hand post Btx-A injections. These patients recovered by 3 and 9 weeks.[6]

Table 3 depicts the McCabe Cold Sensitivity Score from baseline to 4 months post injection. A statistically significant difference was measured as a p-value ≤ 0.050. McCabe Cold Sensitivity Score decreased 39.6 points in the Btx-A group after 4 months ($p = 0.906$). Btx-A group was 0.31 points lower than the control group at the 4-month follow-up ($p = 0.963$). In the Btx-A treatment group, there was a mean change in VAS pain score of 1.44, represented in Table 4. In the placebo group, there was a mean change of 1.83. The difference in mean change between these group is indicated by a p-value of 0.327. VAS pain score in the experimental

group was 0.15 cm higher than the control group after 4 months. The between-arm difference is indicated by a p-value of 0.585.[6]

Table 3. McCabe Cold Sensitivity Score from Baseline to 4 Months Post Injection

	Baseline	4 Months	Mean Change from Baseline	P-value	Mean difference (calculated)
Btx-A	221.79	182.19	39.6	0.906	0.310
Placebo	221.15	182.5	38.65		

Table 4. VAS Pain Score from Baseline to 4 Months Post Injection

	Baseline	4 Months	Mean Change from Baseline	P-value	Mean difference (calculated)
Btx-A	3.43	1.99	1.44	0.327	0.15
Placebo	3.67	1.84	1.83		

Motegi et al. conducted a prospective, single-blind (patients-blind), randomized trial on 45 scleroderma patients with RP over the winter months from 2015 to 2016 at the Department of Dermatology, and Clinical Investigation and Research Unit, Gunma University in Japan. Of the 45 patients, there were 4 males and 41 females with a mean age of 60.7 ± 1.9 years. All patients met the criteria for scleroderma proposed by the American College of Rheumatology. Inclusion and exclusion criteria for selection of patients can be found in Table 1. Twenty-five patients had limited cutaneous type and 20 had diffuse cutaneous type according to LeRoy et al.'s classification.[7] Patients were blinded and randomly selected using the Hope eACReSS system (Fujitsu, Japan) for no-treatment control or treatment of 250 units of Btx-B injections per hand. The hand with the most severe symptoms in each patient was chosen for injection, and 250 units

of Btx was diluted in 2.25 ml saline. Of the 45 patients, only 9 were chosen to receive the 250 units of Btx-B, while the others either received no treatment, 1000 units of Btx-B, or 2,000 units of Btx-B. Injections were performed on the palmar aspect of the hand, as opposed to Bello and Dhaliwal's dorsal approach. VAS pain score (range 0-100 mm) was utilized to assess pain severity after 12 weeks post injection. Adverse events were reviewed at each visit, and none were noted in the treatment group other than mild pain at the injection site that resolved within a few hours. It is unclear whether all patients were accounted for and attributed at its conclusion.[7]

As depicted in Table 5, baseline VAS pain score in the 250-unit Btx-B group was 100%, and at 12 weeks the value decreased to 50%, resulting in a mean change of 50%. On the other hand, control group increased by 25% from baseline. A statistically significant value is indicated by a p-value < 0.05. The mean difference from baseline between these groups was given a p-value < 0.05.[7]

Table 5. VAS Pain Score from Baseline to 12 Weeks Post Injection

	Baseline	12 Weeks	Mean Change from Baseline	P-value	Mean difference (calculated)
Btx-B	100	50	-50%	<0.05	75
Placebo	100	125	+25%		

DISCUSSION

Raynaud's Phenomenon is a debilitating condition, especially for patients with scleroderma. Pharmacological treatments can fail to alleviate symptoms, resulting in ischemia, ulcers, and gangrene, and surgical procedures can lead to severe complications. Botulinum toxin can serve as a non-surgical treatment option for refractory RP. Although rare, there are some complications or side effects that can accompany botulinum toxin. Local side effects include

pain at injection site, ecchymosis, or intrinsic muscle weakness; these effects have proven to be transient in the previous studies discussed. Some systemic complications include nausea, fatigue, flu-like symptoms, diplopia, dysarthria, ptosis, dysphagia, dystonia, urinary incontinence, and rashes.[8] Evidently, these effects are more likely to arise following palmar injections.[7]

This systematic review focuses on the effectiveness of botulinum toxin as a non-invasive alternative therapy for reducing sensory symptoms in the hands of patients with RP. Bello et al. did not provide significant results in McCabe Cold Sensitivity Score or VAS pain score between the hands of Btx-A injection and placebo ($p = 906$ and 0.327, respectively).[6] Although both scores did decrease after 4 months, the reduction was not significant compared to the control group. On the other hand, Motegi et al. demonstrated significant VAS pain scores in patients treated with 250 units of Btx-B after 12 weeks compared to the control ($p < 0.050$).[7] This study shows the effectiveness of Btx-B as a treatment option for pain reduction in RP, proposing that Btx-B accomplishes this through blockage of noradrenaline release, which prevents spasms and vascular contraction. Dhaliwal et al. also demonstrated a significant mean change in VAS pain scores from baseline to 12 weeks ($p = 0.050$).[5]

One limitation within the studies is the number of participants. In Motegi et al., the target group consisted of only 9 participants, whereas Bello et al. and Dhaliwal et al. incorporated 40 patients.[5,6,7] Overall, it would be more beneficial to have a greater sample size within all three studies, providing a more effective representation of the general population. Additionally, types of medications and their dosages prior to treatment vary between the studies, possibly reducing the validity of the results. For example, in Dhaliwal et al., all patients continued their normal medications for RP throughout the study, including calcium channel blockers, iloprost, fluoxetine, PDE-5 inhibitors, and losartan.[5] The length of experiments differ as well. Motegi and

Dhaliwal obtained results at 12 weeks, and Bello gathered information at 4 months (16 weeks).[5,6,7] In the 4-month experiment, botulinum toxin may have worn off in these patients.

A limitation of my own research is the absence of studies on patients with primary RP, as all three of my studies focused on patients with secondary RP. Although patients with primary and secondary RP can differ in severity of their condition and response to treatment, broadening my research to both subsets of RP would expand the generalizability of this systematic review, however, this may sacrifice the precision. Additionally, my results may have been more precise if I solely targeted Btx-A or Btx-B, as there are discrepancies between the two forms of botulinum toxin. Motegi et al. addresses that several clinical studies have proven Btx-B to have a quicker onset of action compared to Btx-A, and furthermore, has a more beneficial effect in treating diseases regulated by the autonomic nervous system.[7] With regards to data comparison, all three studies use different amounts of botulinum for their intervention, and although Motegi splits interventions into 4 sets, I focused on the intervention that was most like the other two studies. This resulted in a target group of only 9 patients receiving 250 units in Motegi's study.[7] Another limiting factor in my selection of journals is that all three studies contain slightly different injection techniques or approaches. Dhaliwal and Bello et al. use dorsal approaches, and in Dhaliwal et al, the author discusses, "Two injections per web space are needed and the injection must be deep feeling the proximal phalanx bone as you inject."[5,6]

CONCLUSION

In this systematic review, Dhaliwal et al. and Motegi et al. provide statistically significant evidence that botulinum toxin reduces sensory symptoms in patients with RP, however, Bello et al. does not demonstrate statistical significance, and therefore, does not support this hypothesis. Based on these outcomes, it cannot be determined whether botulinum toxin improves sensory

symptoms in patients with RP. Although the VAS pain scores significantly decreased compared to the control groups in Motegi et al. and Dhaliwal et al., Bello et al. is the only randomized, double-blind, controlled study, and therefore, is the highest quality study and most reliable to draw a conclusion.

Some considerations are important to take note of with regards to future research studies on botulinum toxin and RP. Larger sample sizes should be implemented in future studies, as this reduces the chance that data will be skewed due to outliers. Also, patients with RP secondary to scleroderma should be selected and compared based on duration of disease, as Bello et al. showed a better response in patients with limited scleroderma and earlier RP (shorter time since RP onset).[6] Future studies should focus on patients with similar medication regimens prior to treatment. Furthermore, these studies should continue the same medications and dosages for every patient or discontinue all medications prior to treatment, in addition to addressing this factor within the study. Lastly, more randomized, double-blind, placebo-controlled studies like Bello et al. should be performed in the future, as this study has served as a basis for future research. More double-blinded RCT studies are imperative to clearly understand the mechanism at which botulinum toxin functions, as well as the best approach in its administration, to improve the quality of life among patients living with Raynaud's Phenomenon.

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