CADTH

CADTH RAPID RESPONSE REPORT: REFERENCE LIST

Botulinum Toxin for Raynaud's Disease: Clinical Effectiveness

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	April 12, 2019
Report Length:	9 Pages

CADTH

Authors: Wendy Pejic, Robin Featherstone

Cite As: Botulinum toxin for Raynaud's disease: clinical effectiveness. Ottawa: CADTH; 2019 Apr. (CADTH rapid response report: reference list).

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Questions or requests for information about this report can be directed to **requests@cadth.ca**

Research Question

What is the clinical effectiveness of botulinum toxin for patients with Raynaud's Disease?

Key Findings

One systematic review, two randomized controlled trials, and five non-randomized studies were identified regarding clinical effectiveness of Botox for patients with Raynaud's Disease.

Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and April 1, 2019. Internet links were provided, where available.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	All patients with Raynaud's disease (also referred to as Raynaud's syndrome/phenomenon)
Intervention	Botulinum toxin (e.g., Botox, may also be referred to botulinum toxin A or B) injection into the affected area of the hands, toes, or feet
Comparators	Any comparator No comparator
Outcomes	Clincial effectiveness (e.g., decreased pain/ulcers in hands) and benefits (e.g., increased function or movement in hands) and safety (e.g., adverse events, harms)
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies

Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, and non-randomized studies.

One systematic review, two randomized controlled trials, and five non-randomized studies were identified regarding clinical effectiveness of Botox for patients with Raynaud's Disease. No relevant health technology assessments or meta-analyses were identified.

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

One systematic review,[1] two randomized controlled trials (RCTs),[2,3] and five non-randomized studies[4-8] were identified regarding clinical effectiveness of Botox for patients with Raynaud's disease/phenomenon (RP). A summary of study characteristics and conclusions are provided in Table 2.

The systematic review[1] did not identify any evidence pertaining to the efficacy of botulinum toxin injection for patients with RP and therefore the authors could not produce conclusions.

Evidence from one RCT[2] did not support the use of botulinum toxin A injection for the treatment of RP in patients with scleroderma. The authors of the other identified RCT[3] observed improvements in digital ulcers and suppressed RP in patients with systemic sclerosis who were injected with botulinum toxin B.

Authors from all of the non-randomized studies observed some sort of clinical effectiveness regarding botulinum toxin A injection.[4-8] In addition, few serious adverse events were noted in the studies.[4-8]

Table 2: Detailed Study Characteristics and Findings of the Included Studies

First Author, Date	Study and Patient Characteristics	Intervention	Comparator(s)	Outcome(s)	Conclusions
Systematic Reviews and Meta-Analyses					
Zebryk, 2016[1]	Patients with RP 11 studies included N=125	Btx-A	NA	• Pain reduction • Healing of digital ulcers	• Insufficient evidence identified to assess Btx-A efficacy in RP
Randomized Controlled Trials					
Bello, 2017[2]	Patients with scleroderma-associated RP N=40 • n=25 had limited scleroderma • n=15 had diffuse	Btx-A (50 units in 2.5 mL sterile saline)	Sterile saline	<u>Primary outcome</u> • Improving blood flow to hands (using Doppler imaging flow data) <u>Secondary</u>	• The evidence does not support the use of Btx-A to treat RP in scleroderma patients • While secondary outcomes indicated some positive effects, their clinical

First Author, Date	Study and Patient Characteristics	Intervention	Comparator(s)	Outcome(s)	Conclusions
	scleroderma			outcomes: • QuickDASH • McCabe Cold Sensitivity Score • Pain on a VAS • Raynaud's Condition Score	meaningfulness is not clear
Motegi, 2017[3]	Patients with systemic sclerosis who have RP N=45	Btx-B • 250 U group • 1,000 U group • 2,000 U group	No treatment	• Pain/number VAS • Raynaud's score • Skin temperature • Digital ulcers	• Btx-B injections (1,000 U and 2,000 U) significantly suppressed RP and digital ulcers • No SAEs
Non-Randomized Studies					
Medina, 2018[4]	Patients with severe RP N=15 3-year retrospective study	Btx-A	NA	• Overall response • Reduction in weekly episodes	• Btx-A is useful treatment for RP with reduction in pain, reduction basal ulcers, and overall patient satisfaction • No SAEs
Weum, 2018[5]	Patients with primary or secondary RP N=10	Btx-A injections in the palm around the radial artery (under ultrasound guidance)	NA	• Vasospastic episodes • Hand temperature • Reduced pain	• Ultrasound allows for precise administration of Btx-A • All patients experienced reduction in pain, warmer hands, and reduced vasospastic episodes • One patient experienced reduced grip strength
Zhang, 2015[6]	Patients in China with RP N=10 Retrospective study	Btx-A (20 U/mL) injection using ultrasound	NA	• Artery flow velocity • Surface temperature • Ulcers • VAS for clinical symptoms	• Btx-A ultrasound-guided injections was associated with improvement in artery flow velocity, improvements in surface temperature, improvement in ulcers and VAS for clinical symptoms • Complications were rarely observed
Chen (Emory University), 2014[7]	Patients with RP N=10 Pilot study	Btx-A injection (40 U)	NA	• Mean digital temperature difference from baseline	No results were provided

First Author, Date	Study and Patient Characteristics	Intervention	Comparator(s)	Outcome(s)	Conclusions
Uppal, 2014[8]	Patients with RP N=20 Prospective study	Btx injection (100 U) into the hand	NA	• Change in pain • Change in appearance • Cold intolerance • Pinch and power grip • Range of movement • DASH score	• Btx appears to be effective for RP secondary to scleroderma • 80% patients reported improvement in symptoms, DASH score, and reduction in pain • 65% reported improvement in cold intolerance • 90% improved their pinch grip while 65% improved their power grip

Btx = botulinum toxin; Btx-A = botulinum toxin type A; Btx-B = botulinum toxin type B; DASH = Disabilities of the Arm, Shoulder and Hand; NA = not applicable; RP = Raynaud's phenomenon; SAE = serious adverse events; VAS = visual analog scale.

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

1. Zebryk P, Puszczewicz MJ. Botulinum toxin A in the treatment of Raynaud's phenomenon: a systematic review. *Arch Med Sci*. 2016 Aug 1;12(4):864-870. PubMed: PM27478469

Randomized Controlled Trials

2. Bello RJ, Cooney CM, Melamed E, 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 Aug;69(8):1661-1669. PubMed: PM28426903

3. Motegi SI, Uehara A, Yamada K, et al. Efficacy of Botulinum toxin B Injection for Raynaud's phenomenon and digital ulcers in patients with systemic sclerosis. *Acta Derm Venereol*. 2017 Jul 6;97(7):843-850. PubMed: PM28358168

Non-Randomized Studies

4. Medina S, Gomez-Zubiaur A, Valdeolivas-Casillas N, et al. Botulinum toxin type A in the treatment of Raynaud's phenomenon: a three-year follow-up study. *Eur J Rheumatol.* 2018 Dec;5(4):224-229. PubMed: PM30501848

5. Weum S, de Weerd L. Ultrasound-guided sympathetic block of the radial artery with Botulinum toxin to treat vasospasm. *Plast Reconstr Surg Glob Open.* 2018 Jul;6(7):e1836.
PubMed: PM30175013

6. Zhang X, Hu Y, Nie Z, et al. Treatment of Raynaud's phenomenon with botulinum toxin type A. *Neurol Sci*. 2015 Jul;36(7):1225-1231.
PubMed: PM25616446

7. Emory University. NCT01233999: Botulinum toxin in the treatment of Raynaud's. *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2014: https://clinicaltrials.gov/ct2/show/study/NCT01233999. Accessed 2019 Apr 11.

8. 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 Oct;39(8):876-880.
PubMed: PM24369360

Appendix — Further Information

Systematic Reviews and Meta-Analyses – Alternative Intervention

9. Herrick A, Muir L. Raynaud's phenomenon (secondary). *BMJ Clin Evid.* 2014 Oct 14;2014.
PubMed: PM25322727

Randomized Controlled Trials – Ongoing

10. University of Central Florida NCT03639766: the effect of Abobotulinum Toxin A on the symptoms of Raynaud's phenomenon. *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2018: https://clinicaltrials.gov/ct2/show/NCT03639766. Accessed 2019 Apr 11.

Review Articles

11. Grando SA, Zachary CB. The non-neuronal and nonmuscular effects of botulinum toxin: an opportunity for a deadly molecule to treat disease in the skin and beyond. *Br J Dermatol*. 2018 May;178(5):1011-1019.
PubMed: PM29086923

12. Guida S, Farnetani F, Nistico SP, et al. New trends in botulinum toxin use in dermatology. *Dermatol Pract Concept*. 2018 Oct;8(4):277-282.
PubMed: PM30479855

13. Matucci-Cerinic C, Nagaraja V, Prignano F, Kahaleh B, Bellando-Randone S. The role of the dermatologist in Raynaud's phenomenon: a clinical challenge. *J Eur Acad Dermatol Venereol*. 2018 Jul;32(7):1120-1127.
PubMed: PM29512213

14. Hughes M, Herrick AL. Raynaud's phenomenon. *Best Pract Res Clin Rheumatol*. 2016 Feb;30(1):112-132.
PubMed: PM27421220

15. Segreto F, Marangi GF, Cerbone V, Persichetti P. The Role of Botulinum toxin A in the treatment of Raynaud phenomenon. *Ann Plast Surg*. 2016 Sep;77(3):318-323.
PubMed: PM26808752

16. Al-Ghamdi AS, Alghanemy N, Joharji H, Al-Qahtani D, Alghamdi H. Botulinum toxin: non cosmetic and off-label dermatological uses. *J Dermatol Dermatologic Surg*. 2015 Jan 1;19(1):1-8. https://doi.org/10.1016/j.jdds.2014.06.002
Accessed 2019 Apr 11.

17. Merritt WH. Role and rationale for extended periarterial sympathectomy in the management of severe Raynaud syndrome: techniques and results. *Hand Clin*. 2015 Feb;31(1):101-120.
PubMed: PM25455361

18. Neumeister MW. The role of botulinum toxin in vasospastic disorders of the hand. *Hand Clin*. 2015 Feb;31(1):23-37.
PubMed: PM25455354

19. Neumeister MW, Webb KN, Romanelli M. Minimally invasive treatment of Raynaud phenomenon: the role of botulinum type A. *Hand Clin*. 2014 Feb;30(1):17-24.
PubMed: PM24286738