Botulinum Toxin for Raynaud’s Disease: Clinical Effectiveness
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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

<table>
<thead>
<tr>
<th>Population</th>
<th>All patients with Raynaud's disease (also referred to as Raynaud’s syndrome/phenomenon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>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</td>
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<tr>
<td>Comparators</td>
<td>Any comparator</td>
</tr>
<tr>
<td></td>
<td>No comparator</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Clinical 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)</td>
</tr>
<tr>
<td>Study Designs</td>
<td>Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies</td>
</tr>
</tbody>
</table>
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 studies4-8 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 review1 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 RCT2 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 RCT3 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

<table>
<thead>
<tr>
<th>First Author, Date</th>
<th>Study and Patient Characteristics</th>
<th>Intervention</th>
<th>Comparator(s)</th>
<th>Outcome(s)</th>
<th>Conclusions</th>
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</thead>
<tbody>
<tr>
<td>Systematic Reviews and Meta-Analyses</td>
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<tr>
<td>Zebryk, 20161</td>
<td>Patients with RP 11 studies included N=125</td>
<td>Btx-A</td>
<td>NA</td>
<td>• Pain reduction • Healing of digital ulcers</td>
<td>• Insufficient evidence identified to assess Btx-A efficacy in RP</td>
</tr>
<tr>
<td>Randomized Controlled Trials</td>
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<tr>
<td>Bello, 20172</td>
<td>Patients with scleroderma-associated RP N=40 • n=25 had limited scleroderma • n=15 had diffuse</td>
<td>Btx-A (50 units in 2.5 mL sterile saline)</td>
<td>Sterile saline</td>
<td>Primary outcome • Improving blood flow to hands (using Doppler imaging flow data) Secondary</td>
<td>• 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</td>
</tr>
<tr>
<td>First Author, Date</td>
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<td>Motegi, 2017&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Patients with systemic sclerosis who have RP N=45</td>
<td>Btx-B • 250 U group • 1,000 U group • 2,000 U group</td>
<td>No treatment</td>
<td>• Pain/number VAS • Raynaud’s score • Skin temperature • Digital ulcers</td>
<td>• Btx-B injections (1,000 U and 2,000 U) significantly suppressed RP and digital ulcers • No SAEs</td>
</tr>
<tr>
<td>Medina, 2018&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Patients with severe RP N=15 3-year retrospective study</td>
<td>Btx-A</td>
<td>NA</td>
<td>• Overall response • Reduction in weekly episodes</td>
<td>• Btx-A is useful treatment for RP with reduction in pain, reduction basal ulcers, and overall patient satisfaction • No SAEs</td>
</tr>
<tr>
<td>Weum, 2018&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Patients with primary or secondary RP N=10</td>
<td>Btx-A injections in the palm around the radial artery (under ultrasound guidance)</td>
<td>NA</td>
<td>• Vasospastic episodes • Hand temperature • Reduced pain</td>
<td>• 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</td>
</tr>
<tr>
<td>Zhang, 2015&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Patients in China with RP N=10 Retrospective study</td>
<td>Btx-A (20 U/mL) injection using ultrasound</td>
<td>NA</td>
<td>• Artery flow velocity • Surface temperature • Ulcers • VAS for clinical symptoms</td>
<td>• 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</td>
</tr>
<tr>
<td>Chen (Emory University), 2014&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Patients with RP N=10 Pilot study</td>
<td>Btx-A injection (40 U)</td>
<td>NA</td>
<td>• Mean digital temperature difference from baseline</td>
<td>No results were provided</td>
</tr>
<tr>
<td>First Author, Date</td>
<td>Study and Patient Characteristics</td>
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</table>
| Uppal, 2014⁶      | 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

Randomized Controlled Trials


Non-Randomized Studies


Appendix — Further Information

Systematic Reviews and Meta-Analyses – Alternative Intervention


Randomized Controlled Trials – Ongoing


Review Articles


PubMed: PM25455354

PubMed: PM24286738