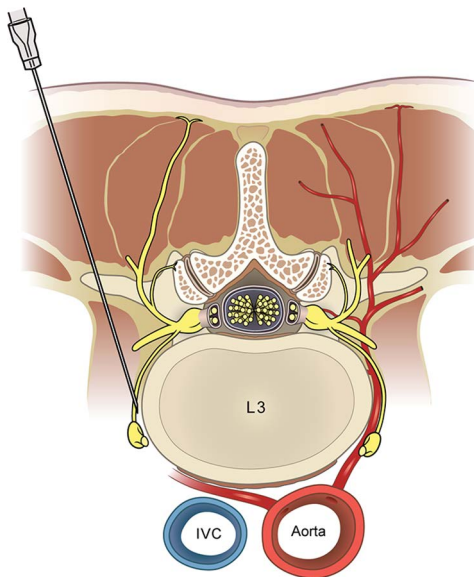


Prolonging Sympathetic Blockade for Complex Regional Pain Syndrome: Is Botulinum Toxin the Answer?

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There are more than a dozen terms denoting “complex regional pain syndrome,” a condition previously known as “reflex sympathetic dystrophy.” The numerous “synonyms” reflect not only its importance in pain medicine (not unlike the linguistic lore that within Eskimo-Aleut languages, there are more than 50 words for snow and sea ice), but also the ambiguity and subjectivity involved in diagnosis. In addition to a quest for standardization, one of the reasons for the name change was the realization that only around 30% of people with reflex sympathetic dystrophy actually had sympathetically-maintained pain, with the identification of sympathetically-maintained pain being contingent on the means of sympathetic blockade (nerve blocks have low specificity compared to phentolamine tests).^{1,2} Compared with diseases, which are characterized by distinct pathophysiologic mechanisms and biomarkers, syndromes merely describe a constellation of signs and symptoms in the absence of other conditions that might explain them; hence, wide variations in the presentation are a hallmark of most. Complex regional pain syndrome type 1, the most common form, is considered by many experts to be part of the new class of nociplastic pain conditions (*e.g.*, fibromyalgia syndrome, irritable bowel syndrome), though it represents an outlier on the spectrum given its prominent physical characteristics.³

In this issue of *ANESTHESIOLOGY*, Yoo *et al.* report the results of their randomized control trial comparing the effects of botulinum toxin type A to levobupivacaine in complex regional pain syndrome patients.⁴ After obtaining informed consent, subjects underwent lumbar sympathetic



“...lumbar sympathetic blocks with botulinum toxin could be a therapeutic alternative for patients with complex regional pain syndrome.”

ganglion block using contrast injection to guide needle placement, with 1.5 ml of 0.5% levobupivacaine administered at both L2 and at L3. Those with a confirmed temperature increase (*i.e.*, 1.5°C or more within 20 min) in the ipsilateral foot were considered eligible for further study procedures, which were conducted the same day. Subjects were then randomized ($n = 24$ in each arm) to receive either botulinum toxin type A in saline or 0.25% levobupivacaine (8 ml divided equally at each of the two injection sites). The primary outcome was the temperature difference in the affected foot compared to the unaffected foot at 1 month, which showed a greater increase in the botulinum toxin group ($1.0 \pm 1.3^\circ\text{C}$ *vs.* $0.1 \pm 0.8^\circ\text{C}$) and was maintained at 3 months.⁴ Although not powered to detect differences in pain, a reduction in mean pain intensity on a 0-to-10 numerical pain scale between groups was noted as well: -2.1 ± 1.0 *versus* -1.0 ± 1.6 , respectively, at 1-month follow-up, and -2.0 ± 1.0 *versus* -0.6 ± 1.6 , respectively, at 3-month follow-up. However, the improvement in cold intolerance symptoms between groups, a common finding in complex regional pain syndrome,⁵ fell shy of statistical significance. The authors concluded that lumbar sympathetic blocks with botulinum toxin could be a therapeutic alternative for patients with complex regional pain syndrome.

While conceptually appealing and grounded in basic science studies demonstrating the potential for sympathetomy to alleviate neuropathic pain,⁶ the study design from Yoo *et al.* raises as many questions as it answers.⁴ The authors chose temperature change as the primary outcome measure

Image: G. Nelson/J. P. Rathmell.

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to ascertain whether botulinum toxin might prolong temperature increase (technical success); however, studies have not found a meaningful correlation between temperature rise and pain relief (clinical success).^{1,7} Since the goal of sympathetic blocks in complex regional pain syndrome is to reduce pain and not elicit temperature increase (though this may alleviate long-term trophic changes such as skin and nail changes that occur secondary to diminished regional blood flow and nutrition), the primary outcome measure essentially represents a surrogate outcome. Whereas complex regional pain syndrome types I and II are clinically indistinguishable and mechanistically similar, most experts consider the former (type I) to be a form of nociplastic pain while the latter meets definitional criteria for neuropathic pain, which may have treatment implications.³ Although less than 15% of patients in the study by Yoo *et al.* had complex regional pain syndrome type II, their outcomes were not stratified by type.⁴

The statistically significant and clinically meaningful improvement in pain scores is also somewhat surprising given that many patients with complex regional pain syndrome do not have sympathetically-maintained pain and would therefore be unlikely to clinically respond to successful sympathetic blockade; comparative-effectiveness studies without a sham group should theoretically require more patients than placebo-controlled studies to detect a difference. The long duration of pain relief observed with botulinum toxin, viewed in the context of multiple studies finding no correlation between temperature change and pain relief; the fact that only a small percentage of those enrolled probably had sympathetically-maintained pain; and clinical and preclinical studies demonstrating benefit for neuropathic pain, suggest that other mechanisms besides sympathetic blockade might be responsible for analgesia.⁸

The requirement for a lower extremity temperature increase before randomization was adroitly employed to ensure that the study blocks would be technically successful (*i.e.*, result in a temperature increase), but the study population was not enriched because pain reduction was not used as an enrollment criterion; therefore, the number of participants with sympathetically-maintained pain who could theoretically benefit from botulinum toxin was fewer than the number enrolled. The rationale for using botulinum toxin is that even sympathetic blocks with a local anesthetic that do provide relief tend to have a very short duration of benefit. In clinical trials, only a tiny percentage provide meaningful relief lasting longer than 4 weeks, and blocks performed with saline provide comparable relief in many people.^{9–11} The quest for more enduring pain relief has led clinicians to investigate chemical and surgical sympathectomy, which provide only limited benefit. In addition to the possibility of weakness and paralysis (*e.g.*, from the spread of neurolytic solutions to spinal and somatic nerves), neuropathic pain (*e.g.*, neuroma), and persistent postsurgical pain (*e.g.*, from tissue injury in high-risk patients with central sensitization),

the interpretation of these studies is compromised by their low quality and lack of any association between outcome and either temperature change or pain relief from diagnostic sympathetic blocks.^{7,12,13} Whereas botulinum toxin represents a potential solution to this dilemma, studies to date have either been small ($n < 10$) or uncontrolled, and the lack of significant complications in a small study designed to determine efficacy do not prove safety.^{14,15}

To date, only one randomized study investigated the use of sympathetic block with botulinum toxin to treat complex regional pain syndrome.¹⁴ In a small ($n = 9$) double-blind, crossover study, Carroll *et al.* found that adding botulinum toxin to bupivacaine resulted in longer pain relief than bupivacaine alone. Although temperatures were not measured in this study, unlike the study by Yoo *et al.*,⁴ this was an enriched population that had previously responded to lumbar sympathetic blockade, making the crossover design more powerful.

So, what are the implications of this study, and how do we move forward? Sympathetic blocks in the cervicothoracic and lumbar regions have demonstrated effectiveness not only for complex regional pain syndrome and non-complex regional pain syndrome conditions characterized by sympathetically-maintained pain, but also a host of other conditions, including, but not limited to: neuropathic pain, hyperhidrosis, cancer-related pain, posttraumatic stress disorder, Raynaud disease, Meniere syndrome, refractory arrhythmias and angina, peripheral vascular disease, certain headaches, and phantom limb pain.^{16,17} Yet, the use of local anesthetic sympathetic blocks for these indications is limited by their short duration of action, which has also hindered clinical research in this area. Whereas botulinum toxin may provide between 2 and 5 months of relief,¹⁸ it will not be effective in all people, and even in responders with chronic sympathetically-maintained pain, it would still likely require multiple repeat procedures. In their study, Yoo *et al.* used relatively low local anesthetic volumes (a total of 3 ml) at two different spinal levels as a selection criterion for enrollment.⁴ However, the volumes of botulinum toxin injected (8 ml), though less than volumes used in some clinical studies and practices,^{19,11} were several-fold greater than those used for the “screening” blocks, which undermines specificity. Given the potentially catastrophic consequences of extravasation of botulinum toxin onto nerves and muscles near the stellate and lumbar sympathetic ganglia (*e.g.*, dysphagia, hoarseness, weakness) and the wide variations in anatomy,^{19,20} greater precision would be needed for widespread use in clinical practice. This could entail using advanced imaging to identify the location of relevant sympathetic ganglia and/or a significant reduction in block volumes, which may increase the likelihood of missing neural targets.

But the 800-lb gorilla in the room encountered when trying to sift through the hundreds of clinical studies evaluating botulinum toxins may be the effect of industry

sponsorship. Botulinum toxins have been reported to be effective for literally dozens of medical indications, including a wide array of ophthalmologic, neurologic, gastrointestinal, urologic, orthopedic, dermatologic, dental, secretory, painful, cosmetic, and even psychiatric indications, amongst others.^{21,22} However, caution must be exercised as independent systematic reviews have found significant discrepancies between industry- and non-industry-sponsored studies evaluating the neurotoxin,^{23,24} which may be even greater than for other products.²⁵ So, while the elegant study by Yoo *et al.* provides a framework for conducting future research, it is but one piece of a yet-to-be completed puzzle.

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Competing Interests

Dr. Singh is a consultant for Releviate (San Diego, California). Dr. Cohen is a consultant for SPR Therapeutics (Cleveland, Ohio), Scilex (San Diego, California), Persica (Canterbury, Kent, UK), Releviate, and SWORD Health (Porto, Portugal).

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