Finlayson HC, O'Connor RJ, et al. Botulinum Toxin injection for management of thoracic outlet syndrome: A double-blind, randomized, controlled trial. Pain 2011;152:2023-2028.

Design: Randomized clinical trial

Study question: does botulinum toxin (BTX) injection alleviate the pain symptoms of thoracic outlet syndrome?

Population/sample size/setting:

- 38 patients (31 women, 7 men, mean age 37) treated for thoracic outlet syndrome (TOS) at a university department of physical medicine in British Columbia
- Patients were referred by other physicians for TOS management and had to meet 3 of these 4 criteria for the clinical diagnosis
    - History of pain and/or paresthesias in the medial arm, forearm, and/or hand
    - Aggravation of symptoms when the hand is elevated
    - Tenderness over the brachial plexus near the clavicle
    - A positive Elevated Arm Stress Test
- Inclusion criteria for those who had the clinical diagnosis were symptoms present for at least 6 months, age at least 19, general medical stability, and prior RMG studies plus either CT or MRI to rule out other diagnoses
- Exclusion criteria were prior treatment with BTX-A, allergy to BTX, history of botulism, myasthenia gravis, or Eaton-Lambert syndrome, prior scalenectomy, use of anticoagulants, and surgery for TOS scheduled within the next 6 months

Main outcome measures:

- All patients had a single injection of the anterior and middle scalene muscles
- Randomization was to injection with 75U of BTX-A in 0.75cc of saline (n=20) or to injection with 0.75 CC of saline alone (n=18)
- No differences in sensation of the injection were noted between the two groups
- Outcomes were measured at 6 weeks, 3 months, and 6 months after the injections
- Primary outcome was VAS pain on a 100 mm scale at 6 weeks, since that is consistent with the expected duration of action of BTX
- Secondary outcomes were VAS for paresthesias, the Disabilities of Arm, Shoulder, and Hand (DASH) scores, and the SF-36 physical and mental scores
- The study was powered to detect a group difference treatment effect of 20 mm on the 100 point VAS, and this was considered the minimally important effect size for changes in VAS from baseline to 6 weeks

- All patients were asked to report any adverse event during the study, including injection site pain, bleeding, dysphagia, changes in pain and paresthesias, dyspnea, and new muscle weakness
- Median VAS pain at baseline was 46 for BTX and 63 for placebo; 6 of the 20 BTX patients had a VAS less than 30 mm, but 2 of 18 placebo patients had a VAS<30
- Change scores at 6 weeks differed by less than the minimal clinically important difference of 20 points; the group difference in change scores was -5.03 points in favor of BTX, but the 95% confidence interval was between -15.7 and +5.7, which includes the null value of 0 points
- Only 4 patients reported a 50% decrease in pain at 6 weeks: 3 in the BTX group and 1 in the placebo group
- Similarly, the secondary outcomes of VAS paresthesia, DASH, SF-36 mental, and SF-36 physical showed no differences between groups

Authors' conclusions:

- BTX injection fell short of the predefined difference in pain of 20 mm, and BTX did not show a clinically or statistically significant treatment effect
- There were some limitations in the study
    - The patients had had symptoms for an average of 6 years in the BTX group and 3 years in the placebo group, and could have developed chronic pain syndromes with central sensitization
    - The allocation concealment may have been compromised by having had the allocation list covered with an opaque piece of paper in a file drawer rather than sealed in an opaque envelope, and the person preparing the syringes (not the injector) was aware of its contents, which could have compromised the blinding
- It is likely that BTX does not provide clinically important relief to patients with a long duration of neurogenic TOS, who may have developed a chronic pain syndrome

Comments:

- The study is powered only enough to detect a fairly large (1 standard deviation) effect size
- The lower pain VAS at baseline for the BTX group, and the fact of having 6 patients already with pain scores less than 30 points, could create a floor effect for achieving a 20 point treatment effect, and this could be part of the reason that a larger effect size was not found; this could weaken the strength of the conclusion that BTX has no effect
- The compromise of allocation concealment and of blinding would probably not undermine the study results, since these are more likely to inflate rather than underestimate treatment effects with placebo controls

- The chronicity of the symptoms is, as the authors propose, likely to define a population with a chronic pain syndrome, and the duration of symptoms in the BTX group was longer than in the placebo group

Assessment: adequate for some evidence that BTX in a dose of 75U injected into the scalene muscles does not differ appreciably from an injection of placebo in patients with TOS of several years' duration