
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.