

Ranoux D, Attal N, et al. Botulinum Toxin Type A Induces Direct Analgesic Effects in Chronic Neuropathic Pain. Ann Neurol 2008;64:274-284.

Design: Randomized clinical trial

Population/sample size/setting:

- 29 patients (19 women, 10 men, mean age 52) treated for neuropathic pain in a university neurology service in Limoges, France
- Inclusion criteria were at least 6 months of daily pain (pain score at least 3 out of 10), limited area of pain (not exceeding 60 cm²), with mechanical allodynia in the painful area
- Exclusion criteria were neuromuscular junction disease, hypersensitivity to botulinum toxin A (BTX), other painful conditions, major depression, history of drug or alcohol abuse, litigation or compensation claim, and facial pain

Main outcome measures:

- Randomized to BTX (n=15) or saline placebo (n=14)
- All patients received intradermal injections at an average of 20 separate sites; approximately equal volumes (4.4 ml of BTX and 3.9 cc of placebo) were injected, and the dose of BTX ranged from 20 to 190 units
- Primary outcome measure was the change in the weekly averages of daily pain scores (from patient diaries) between baseline and 24 weeks
- 22 of 29 patients completed 24 weeks of follow-up; 1 patient (BTX) dropped out in the first 12 weeks due to lack of efficacy; between 12 and 24 weeks, 2 BTX patients (1 lack of efficacy, 1 intercurrent condition) and 4 placebo patients (lack of efficacy) withdrew from the study
- Pain intensity improved weekly in the BTX group in comparison with the placebo group, starting at week 2, increasing thereafter for 4 weeks and remaining stable for up to 14 weeks
- At week 12, the mean percentage pain relief in the BTX group was 33% vs. 7.7% in the placebo group; at week 24, the mean percentage pain relief scores for BTX and placebo were 25.3% and 7.6%
- At week 12, 6 BTX patients had 50% or more pain relief compared to 1 placebo patient; increases in pain scores were seen in 2 BTX and 7 placebo patients
- Exploratory analyses suggested that preservation of thermal sensation at baseline was associated with better analgesic response to BTX
- No patient was able to recognize the difference between BTX and placebo based on side effects; the only adverse effects occurred at the time of injection, and were related to pain with the injections

Authors' conclusions:

- Intradermal injection of BTX has direct analgesic effects in patients with focal chronic neuropathic pain with allodynia
- The injections were done in patients in whom the area of pain is limited, and was done according to procedures used for hyperhidrosis

- Some quality of life measures, used as secondary outcomes, also were better in BTX than in placebo patients
- BTX is well-tolerated and should be considered at part of the therapeutic arsenal in against focal neuropathic states

Comments:

- Randomization, concealment of allocation, and blinding were all reported and appeared to be successful; risk of bias is low
- The mean pain improvements are highly skewed (standard deviations very large in relation to the mean), and not well suited for the t-tests which were used to compare them; the percentage of 50% responders and the percentage of patients with worsening of pain scores are probably better comparisons of treatment effect
- The number of patients is small, and the results may be impractical to replicate in patients with pain over a larger area than the 60 cm² which was the upper limit for entry into this study
- For such small focal neuropathic pain sites, other focal treatments may be more convenient

Assessment: Adequate for evidence that intradermal botulinum toxin may relieve focal neuropathic pain for 12 weeks and possibly up to 24 weeks, but irrelevant for patients whose area of involvement is greater than 60 cm²