
Design: Meta-analysis of randomized clinical trials

PICOS:
- **Patients:** Adults with nonradicular neck pain and cervicogenic headache, excluding neck disorders with long tract signs and from other pathological entities, headache when neck pain was not a dominant feature, radicular neck pain, and whiplash disorders
- **Intervention:** Botulinum toxin (BoNT-A) intramuscular injections given with the intention of alleviating neck pain
- **Comparison:** Placebo injection or other active treatment (e.g., ultrasound), or botulinum toxin plus an adjunctive treatment vs. the same adjunctive treatment alone
- **Outcomes:** Patient-reported pain relief, function, and disability; observer-based physical function based on standardized testing and scoring procedures; patient satisfaction or quality of life
- **Study types:** Randomized and quasi-randomized (e.g., possibly biased allocation based on non-random criteria such as odd-even numbers, day of week, patient record, or social security number)

Study search and selection:
- Electronic databases included Cochrane Central Register, MEDLINE, CINAHL, EMBASE, Index to Chiropractic Literature, LILACS (Latin-American and Caribbean literature), and AMED (Allied and Complementary Medicine)
- Other efforts to identify relevant trials came from references, conference proceedings, personal communication with content experts
- At least two authors independently screened studies for inclusion and for risk of bias, resolving disagreements by group consensus decisions
  - Risk of bias assessment based on randomization, concealment of allocation, blinding, attrition, baseline similarity of groups, absence of selective outcome reporting
- Clinical relevance was judged based on adequate descriptions of patients and interventions, reporting of pertinent outcomes, size of benefits, and whether benefits are worth potential harms
  - For pain, minimum clinically important difference was 10 points on a 100 point scale
  - For outcomes compared on the basis of standard mean differences between groups, a difference of 0.2 standard deviations was small, 0.5 SD was medium, and 0.8 SD or more was large
- Quality of evidence was based on estimates of whether further research is likely to change confidence in the estimate of treatment effect, depending on
study design, risk of bias, inconsistency of results, indirectness (not generalizable), imprecision (insufficient data), and reporting biases

- High quality evidence—further research unlikely to change confidence of estimate of effect; consistent results in studies with low risk of bias, with sufficient data and narrow confidence intervals (all quality domains are met)
- Moderate, low, very low, and no evidence reflected failure of more quality domains, with increasing lack of confidence that future research will alter estimate of treatment effect

Results:
- Clinical heterogeneity between studies was assessed prior to calculating any pooled effect measures
  - Issues such as symptom duration (subacute vs. chronic), subtype of neck pain, characteristics of treatments, and measured outcomes (pain, function, quality of life)
- 8 studies were included in a meta-analysis, and 1 additional study was included in a qualitative synthesis
- 7 studies examined subacute or chronic neck pain with a myofascial component, and 2 studies examined cervicogenic headache
- There was high-quality evidence from 5 trials (252 patients) that BoNT-A and placebo did not differ in short-term (4 weeks) neck pain relief without neurological findings
- There was low-quality evidence from one trial that there was no difference between BoNT-A and placebo for intermediate-term (6 months) neck pain relief
- Other outcomes were rated as very low-quality evidence, and most of these did not show a difference between BoNT-A and control treatments
- Two studies of cervicogenic headache were reported, both with high risk of bias; only one of these reported results which could be extracted for estimating treatment effect, and it showed no differences between BoNT-A plus exercise/medication and saline plus exercise/medication
- Adverse events were inconsistently reported across studies, but most were described as transient and not disabling; in 90% of study results, authors judged that the benefits were not worth the potential harms of BoNT-A injection

Authors’ conclusions:
- Current evidence suggests that there is not a clinically or statistically significant benefit of BoNT-A in the treatment of chronic neck pain in the short term
- Cervicogenic headache has very low quality evidence from which to estimate the effectiveness of BoNT-A
- There may be issues of dosage and administration of BoNT-A which were not resolved by the available evidence
- One study which purported to show an effect of BoNT-A reported superior pain resolution at 5-8 weeks but not before or after; this is unlikely to represent a true effect of BoNT-A, since such a time-specific effect does not make clinical sense.

- Although future research is unlikely to change the estimate of BoNT-A as a stand-alone treatment, it may be profitable to investigate its use in combination with other interventions and to try to identify potential subgroups of patients who may benefit from its use.

Comments:

- Only one study of cervicogenic headache (Schnider 2002) had data which was extractable for a quantitative estimate of pain intensity, and it showed no difference between BoNT-A and placebo.

- Linde 2011 reported treatment effects as changes from baseline in pain intensity, and Schnider 2002 reported results as mean pain intensity after injection.

- Because effects were reported as standard mean differences, it is possible to combine the results of Schnider 2002 and Linde 2011, calculating standard errors for Linde 2011 from the 95% confidence intervals and the standard deviations from the numbers of patients reported to have received each injection; the pooled estimate of BoNT-A effect is clinically and statistically non-significant.

Assessment: Good evidence that botulinum toxin is not different from placebo for cervical pain
Adequate evidence that botulinum toxin is not likely to be clinically more effective than placebo for cervicogenic headache.