UPDATE ON Craniofacial Pain and Dystonia
BOTULINUM TOXIN THERAPY FOR CERVICOCGENIC HEADACHE AND NECK PAIN

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Objectives

- Discuss mechanism of action of botulinum toxin
- Provide information on botulinum toxin and neck pain
- Review data on botulinum toxin and neck pain syndromes
- Provide data on botulinum toxin and Cervicogenic headache
Normal Neurotransmitter Exocytosis

**Normal Neurotransmitter Release**

- **SNARE Proteins Form Complex**
- **Vesicle and Terminal Membranes Fuse**
- **Synaptic Fusion Complex**
- **Neurotransmitter Released**

**NERVE TERMINUS**

- **SNAP-25**
- **Syntaxin**
- **Synaptobrevin**
- **SNARE Proteins**

**SYNAPTIC CLEFT**

- **Acetylcholine**
- **Acetylcholine Receptor**

**MUSCLE CELL**

- **Muscle Fiber Contracts**

Reproduced with permission from Arnon SS, et al.*JAMA.* 2001; 285:1061
Neurotransmitter Exocytosis: Intracellular Inhibition with BoNT

- Botulinum Toxin Endocytosed
- Light Chain Cleaves Specific SNARE Proteins
  - Types B, D, F, G
  - Types A, C, E
  - Type C

- SNARE Complex Does Not Form
- Membranes Do Not Fuse

- Neurotransmitter Not Released

Botulinum Toxin Prevents Peripheral Sensitization (direct) and Central Sensitization (indirect)

Prevents:
- Release of Glutamate, CGRP, SP
- Peripheral Sensitization
- Formalin Phase II pain
- TRPV1 expression

Indirectly Prevents:
- Central Sensitization
- c-Fos expression
- Receptive field expansion
- Allodynia
Botulinum toxin and neck pain

- Botulinum toxin is studied for neck pain for the following states:
  - Cervical Dystonia
  - Whiplash injury
  - Myofacial pain syndrome (MPS)
  - Chronic neck pain
  - Cerviogenic Headache
Neck pain in Cervical Dystonia

• 4 commercially available botulinum toxin preparations are approved for Cervical Dystonia (CD)
• Pain is a significant component of CD
  – seen in 75% of patients with CD
• Pivotal studies for each of the toxins show reduction in neck pain as a component of CD
CD & Pain

• Myobloc - Rimabotulinum toxin B
  – Pain reduction vs placebo seen in pivotal trials\(^1,2\)
  – Pain reduction vs active comparator (Botox) \(^3\)

• Botox - Onabotulinum toxin A
  – CD Probe registry\(^4\): 733 /1046 patients with moderate severe neck pain
  – 67-72% reduction in pain noted 4-6 weeks after each injection cycle on multiple scales.
  – Onset of pain reduction approximately 7 days

3. Lew, M Chinnapongse, R et al Int J of Neuroscience 2010;120:298-300
• **Dysport - Abobotulinum toxin A:**
  – Reduction in TWSTRS pain score\(^1\)
• **Xeomin - Incobotulinum toxin A**
  – Reduction in TWSTRS pain score\(^2\)

\(^1\) Dysport Pivotal Study
\(^2\) Xeomin Pivotal Study
• Various neck pain syndromes are due to muscle hyperactivity, inappropriate release of acetylcholine or tenderness of neck muscles
• Muscle relaxants and trigger points with local anesthetics or steroids have been used with partial response
• Botulinum toxin is a neuromuscular blocking agent, reduces excessive muscle tone, and reduce nociceptive input.
Whiplash Injury

- Neck injury related to acceleration / deceleration injury of head
- Approximately 200,000 cases per year
- Local symptoms: neck, arm, shoulder and back pain
- Other symptoms: headache, paresthesia, difficulty focusing
Whiplash injury and Botulinum Toxin

- Double blind, placebo controlled
- 26 subjects
- BTX-A, 100 units in cervicothoracic muscles
- Outcome measures: total subjective neck, shoulder, and head pain based on visual analog scales; objective total range of neck motion (ROM) at 2 & 4 weeks
- Improvement in pain at 4 weeks (p<0.01)

- 22 patients (2-48 weeks after WI)
- Randomized to Botox 200 units Vs Placebo
- Outcome: VAS and 5 point Verbal Rating Scale
- Results: Improvement in both groups, greater improvement in Botox group but not statistically significant
- Larger study is needed to better evaluate
Whiplash: Review Article

- 36 studies looking at mechanical neck disorders including whiplash studies
- review of multiple treatment interventions (NSAIDs, steroids, anesthetics, botulinum toxins)
- Moderate evidence that botulinum toxin are not effective for mechanical neck disorders
- Pitfall: no consistent study design or outcomes measured
Myofacial Pain Syndrome

- Chronic pain disorder
- Due to repeated muscle contractions
- Due to hobbies, work, or repetitive motion
- Pressure sensitive trigger points
- Typical therapy: Physical therapy, analgesic and trigger point injections
# Myofacial Pain Syndrome and Botulinum Toxin

<table>
<thead>
<tr>
<th>Article</th>
<th>Study Groups</th>
<th>Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrante et al (Anesthesiology 2005)</td>
<td>Saline vs 50, 125 or 250 units of Botox divided into 5 trigger points</td>
<td>VAS, need for rescue pain medication and pressure algometry</td>
<td>No additional improvement in Botox group</td>
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<td>Grabowski et al (Pain2005)</td>
<td>18 patients: 200 units Botox vs Bupavicaine Randomized Cross over</td>
<td>VAS, time to 75% return of pain</td>
<td>Both groups improved, no significant improvement in Botox group</td>
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<tr>
<td>Ho et al (E J Pain2007)</td>
<td>Systematic review of 5 trials comparing Botox vs Trigger point injections</td>
<td>Oxford Pain Validity Scale</td>
<td>1 study showed benefit, 4 studies did not show benefit</td>
</tr>
<tr>
<td>Ojala (J MSK Pain 2010)</td>
<td>31 patients: Saline or 15-35 units of Botox</td>
<td>Soft tissue stiffness measure,, pressure pain threshold, subjective severity of neck shoulder pain</td>
<td>No Significant improvement</td>
</tr>
<tr>
<td>Davis (The Btx J 2011)</td>
<td>12 patients w MPS randomized to saline vs Botox. 11 patients with CD in Botox group</td>
<td>Pain diary measurement</td>
<td>No significant improvement</td>
</tr>
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</table>
Myofacial Pain and Toxin: Review

- Reviewed articles on Myofacial pain, trigger points and botulinum toxin
- Multiple studies with contradictory results
- Differences between diagnostic criteria, outcomes, dose and dilution and location of injection
- Treatment cannot be recommended or rejected
- Botulinum toxin injection may be helpful in refractory cases

- 47 subjects with refractory neck pain (no acute pathology)
- Exclusion: CD, prior toxin treatment
- Botox dose 150 - 300 units (splen cap, trapezius, rhomboids)
- Results: VAS significant improvement in Botox group. 6 excellent responders with > 50% in VAS, > 30% reduction in pain.
Cervicogenic Headache

- Secondary Headache due to neck illness or lesion
- Diagnostic criteria:
  - A: Pain, referred from a source in the neck and perceived in one or more regions of the head and/or face, fulfilling criteria C and D
  - B: Clinical, laboratory and/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck known to be, or generally accepted as, a valid cause of headache
  - C: Evidence that the pain can be attributed to the neck disorder or lesion based on at least one of the following:
    - 1: demonstration of clinical signs that implicate a source of pain in the neck
    - 2: abolition of headache following diagnostic blockade of a cervical structure or its nerve supply using placebo- or other adequate controls
  - D: Pain resolves within 3 months after successful treatment of the causative disorder or lesion

*http://ihs-classification.org/en/02_klassifikation/03_teil2/11.02.01_cranial.html
Intradermal Botulinum Toxin, Type B, for Treating Migraines of Cervical Origin

Krusz JC. Intradermal botulinum toxin type B for migraine of cervical origin. Poster presented at: 22nd Annual Scientific Meeting of the American Pain Society; March 20-23, 2003; Chicago, IL

- Double blind, placebo controlled
- 40 Subjects with migraines “of cervical origin”
- BTX-B 2,500 units, 5,000 units vs. placebo
- Intradermal injection over sites of greater and lesser occipital nerves
- Followed for 3 months
- Reduction in headache frequency (p<0.01)
- Reduction in headache severity
  - 2,500 units (p<0.01)  5,000 units (<0.02)
## Placebo Controlled Studies

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<td>Schneider (Neurology 2001)</td>
<td>33 patients: 16 patients 90 units Botox &amp; 17 patients saline at 6 txt</td>
<td>Home diary, Trigger point tenderness score</td>
<td>Active group: + improvement not statistically significant. No weakness</td>
</tr>
<tr>
<td>Linde (Cephalgia 2011)</td>
<td>Randomized placebo cross over. 28 patients: fixed dose of Botox vs placebo</td>
<td>Headache Calendar, QOL questionnaire, neck mobility measures</td>
<td>No significant improvement regarding primary or secondary measures</td>
</tr>
<tr>
<td>Stillman (Neurology 2006)</td>
<td>Randomized double blind placebo controlled trial</td>
<td>Reduction of frequency &amp; severity of cervicalgia &amp; headache</td>
<td>No significant difference in primary outcome between 2 groups</td>
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Cervicogenic Headache

- 3 placebo controlled trials have not show benefit
- Cervicogenic headache is a diverse condition with diverse sources of pain*
- Trials differ by injection dose, injection site, and measures*
- While placebo controlled trials do not show benefit, earlier studies have shown benefit
- In the meantime, “keep an open mind” on the role of botulinum toxin in cervicogenic headache.*
Summary

• The role of botulinum toxin has been evaluated in Cervical Dystonia and Cervical Dystonia related neck pain
• Botulinum toxin reduces the release of central CGRP
• There are mixed study results in various neck pain conditions (MPS, Whiplash pain syndrome, chronic neck pain and Cervicogenic headache) refractory to standard therapy
• Further studies with standardized injections and measures are needed to further study the role of botulinum toxin in these conditions.
Thank you!