Botulinum Toxin Therapy for Myofascial, Cervical Thoracic Pain

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Disclosures

- Consultant/independent contractor: Allergen plc, and Ipsen Biopharmaceuticals, Inc.
- Speaker’s Bureau: Allergan plc, Avanir Pharmaceuticals, Inc. Depomed Inc., and Ipsen Biopharmaceuticals, Inc.
- I intend to reference off-label use of the following products:
  - Dysport (Ipsen)
  - Myobloc (US WorldMeds)
  - Botox (Allergan)
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
- Discuss data on Thoracic Outlet Syndrome
- Provide data on botulinum toxin and Cervicogenic headache
Normal Neurotransmitter Exocytosis

A Normal Neurotransmitter Release

SNARE Proteins Form Complex

Vesicle and Terminal Membranes Fuse

NERVE TERMINUS

SNARE Proteins
- Synaptobrevin
- SNAP-25
- Syntaxin

SYNAPTIC CLEFT

Acetylcholine

Acetylcholine Receptor

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

Reproduced with permission from Arnon SS, et al. JAMA. 2001; 285:1061
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)
  - Thoracic outlet syndrome (TOS)
  - Cervicogenic 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

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
- Pathophysiology
Whiplash Injury and Botulinum Toxin

- "Treatment of whiplash associated neck pain with botulinum toxin-A: a pilot study"
- 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)

The Analgesic Effect of Botulinum toxin A on Post whiplash Neck Pain

- 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

- “Medicinal and injection therapies for mechanical neck disorders" 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</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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<tr>
<td>(Anesthesiology 2005)</td>
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<tr>
<td>Grabowski et al</td>
<td>18 patients: 200 units Botox vs Bupivicaine Randomized Cross over</td>
<td>VAS, time to 75% return of pain</td>
<td>Both groups improved, no significant improvement in Botox group</td>
</tr>
<tr>
<td>(Pain2005)</td>
<td></td>
<td></td>
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<tr>
<td>Ho et al</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>(E J Pain2007)</td>
<td></td>
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<tr>
<td>Ojala</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>(J MSK Pain 2010)</td>
<td></td>
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</tr>
<tr>
<td>Davis</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>
<tr>
<td>(The Btx J 2011)</td>
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“Botulinum Toxin for the Treatment of Myofascial Pain Syndromes Involving the Neck and Back: A Review from a Clinical Perspective”

Reviewed articles on Myofascial 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

Botulinum Neurotoxin-A for Treatment of Refractory Neck Pain: A Randomized, Double Blind Study

47 subjects with refractory neck pain (no acute pathology)

Exclusion: CD, prior toxin treatment

Botox dose 150 - 300 units (spl 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

- 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)

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
## Data

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<tr>
<td>Schneider</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</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</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>
</tr>
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</table>
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.*

Thoracic Outlet Syndrome (TOS)

- Compression of nerves & blood vessels between the clavicle and first rib
- Common causes: trauma, cervical rib, overuse / repetitive injury
- Symptoms of shoulder / neck pain and paresthesia in the fingers
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<td><strong>Jordan</strong> (Ann of Vasc surg 2000)</td>
<td>Placebo vs Botox</td>
<td>101 point questionnaire</td>
<td>14/22 had 50% reduction in Botox group vs 4/22 had 50% reduction in placebo</td>
</tr>
<tr>
<td><strong>Finlayson</strong> (Pain 2009)</td>
<td>38 patients, Randomized trial: Botox vs Placebo</td>
<td>VAS &amp; pain questionnaires</td>
<td>Statistically significant reduction in VAS in Botox group vs Placebo</td>
</tr>
<tr>
<td><strong>Danielson</strong> (Am J of Phy Med Rehab 2008)</td>
<td>Case Report</td>
<td>Doppler Ultrasound</td>
<td>15 units of Botox injected into right anterior scalene improved doppler ultrasound flow</td>
</tr>
</tbody>
</table>
Guidance

- Ultrasound
  - Ultrasound guided injections to Scalenes, Pectoralis Minor and Subclavious are safe, well tolerated and beneficial
  - Torriani: Skeletal Radiology 2010
- EMG / Ultrasound / Fluoroscopy
  - Comparison of 2 different guidance techniques
  - 77/245: Ultrasound & EMG vs 168/245: EMG and Fluoroscopy
  - No significant difference in complication rate or benefit between the two guidance techniques
- Jordan: Pain Physician 2007
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.

There is positive preliminary data on TOS but better studies need to be designed on muscle selection and dosing.

Further studies with standardized injections and measures are needed to further study the role of botulinum toxin in these conditions.