Botulinum Toxin Injection Patterns, Complications, and Adjunctive Therapies

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Overview

• Background
• Mechanism of Action
• Types of Botulinum Toxin
• Treatment
  • Pre-treatment
  • Pattern
  • Safety
• Causes of decreased efficacy
• Adjunctive Therapy
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What is Botulinum Toxin?

• Clostridium botulinum is a type of bacteria which produces ubiquitous spores which release toxins that can impact the nervous system.

• In the early 1980s the first ophthalmic application of botulinum toxin was employed to treat eye movement issues.

• Late 1980s the purified toxin was approved by the FDA for the treatment of blepharospasm
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Mechanism of Action

A. Normal Neurotransmitter Release
- SNARE Proteins Form Complex
- Vesicle and Terminal Membranes Fuse
- Neurotransmitter Released
- Acetylcholine Released
- Acetylcholine Receptor
- Muscle Fiber Contracts

B. Exposure to Botulinum Toxin
- 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
- Muscle Fiber Paralyzed

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## Types of Botulinum Toxin

<table>
<thead>
<tr>
<th></th>
<th>OnabotulinumtoxinA</th>
<th>AbobotulinumtoxinA</th>
<th>IncobotulinumtoxinA</th>
<th>RimabotulinumtoxinB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>US Tradename</strong></td>
<td>Botox®</td>
<td>Dysport®</td>
<td>Xeomin®</td>
<td>Myobloc®</td>
</tr>
<tr>
<td><strong>Company</strong></td>
<td>Allergan, Inc.</td>
<td>Ipsen Inc./Medicis</td>
<td>Merz Pharmaceuticals</td>
<td>Solstice Neurosciences Inc./Eisai Co., Ltd.</td>
</tr>
<tr>
<td><strong>Active substance</strong></td>
<td>BoNT-A complex</td>
<td>BoNT-A complex</td>
<td>BoNT-A free from complexing proteins</td>
<td>BoNT-B complex</td>
</tr>
<tr>
<td><strong>Molecular weight</strong></td>
<td>900 kDa</td>
<td>500–900 kDa</td>
<td>150 kDa</td>
<td>700 kDa</td>
</tr>
<tr>
<td><strong>Target protein</strong></td>
<td>SNAP-25</td>
<td>SNAP-25</td>
<td>SNAP-25</td>
<td>VAMP</td>
</tr>
<tr>
<td><strong>Units per vial</strong></td>
<td>50 or 100</td>
<td>300 or 500</td>
<td>100</td>
<td>2500, 5000, or 10000</td>
</tr>
<tr>
<td><strong>Pharmaceutical form</strong></td>
<td>Powder</td>
<td>Powder</td>
<td>Powder</td>
<td>Solution</td>
</tr>
<tr>
<td><strong>US FDA-approved Indications</strong></td>
<td>Blepharospasm, cervical dystonia, glabellar lines, hyperhidrosis, chronic migraine</td>
<td>Blepharospasm, cervical dystonia, glabellar lines</td>
<td>Blepharospasm, cervical dystonia, glabellar lines</td>
<td>Cervical dystonia</td>
</tr>
<tr>
<td><strong>Storage temperature before and after reconstitution</strong></td>
<td>2–8°C/2–8°C</td>
<td>2–8°C/2–8°C</td>
<td>&lt;25°C/2–8°C</td>
<td>2–8°C/2–8°C</td>
</tr>
</tbody>
</table>
DaxibotulinumtoxinA for Injection for the Treatment of Glabellar Lines: Efficacy Results From SAKURA 3, a Large, Open-Label, Phase 3 Safety Study

Sabrina G. Fabi, MD,* Joel L. Cohen, MD,† Lawrence J. Green, MD,‡ Sunil Dhawan, MD,§ Theda C. Kontis, MD,‖ Leslie Baumann, MD,¶ Todd M. Gross, PHD,** Conor J. Gallagher, PHD,** Jessica Brown, PharmD,** and Roman G. Rubio, MD**
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Pre-treatment & Preparation
Impact on treatment

Efficacy of Botulinum Toxin Type A After Topical Anesthesia


*Plastic Eye Surgery Associates, PLLC, Houston, Texas, U.S.A.; †University of Texas, Houston, Texas, U.S.A.; and ‡Baylor College of Medicine, Houston, Texas, U.S.A.

TABLE 2. Patient-reported outcomes of botulinum toxin type A injection efficacy with topical anesthetic versus placebo cream

<table>
<thead>
<tr>
<th></th>
<th>Anesthetic-treated side</th>
<th>Placebo-treated side</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blepharospasm patients identifying a better effect from botulinum toxin type A on one side of the face (n = 48 trials)</td>
<td>6 (12.5%)</td>
<td>42 (87.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cosmetic patients identifying a better effect from botulinum toxin type A on one side of the face (n = 46 trials)</td>
<td>4 (9%)</td>
<td>42 (91%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Impact on treatment

Botox: Shaken, Not Stirred

Nadia A. Kazim, M.D., and Evan H. Black, M.D.

Department of Ophthalmology, Kresge Eye Institute, Wayne State University School of Medicine, Detroit, Michigan, U.S.A.

Purpose: To determine whether the effect of botulinum toxin type A is maintained and has the same duration when it is reconstituted vigorously.

Methods: A prospective, double-blinded, randomized study was performed on 7 consecutive patients who underwent botulinum toxin type A injections to the forehead by one oculoplastic surgeon. Half of each patient’s forehead was injected with botulinum toxin type A that had been gently reconstituted according to the package insert and the other half of the forehead was injected with botulinum toxin type A that had been reconstituted vigorously. Eyebrow excursion was measured in millimeters before injection, 1 week after injection, and every month after injection up to a total of 6 months.

Results: Seven consecutive patients with an average age of 39.9 ± 2.8 years were evaluated. There was no statistically significant difference in eyebrow excursion between the side of the forehead that had been injected with gently reconstituted botulinum toxin type A and the side that had been injected with vigorously reconstituted botulinum toxin type A at every visit.

Conclusion: The effect of botulinum toxin type A is maintained and has the same duration when it is reconstituted vigorously compared with when it is reconstituted gently.
Investigating the Efficacy of Vibration Anesthesia to Reduce Pain From Cosmetic Botulinum Toxin Injections

Pooja Sharma, MD; Craig N. Czyz, DO, FACOS; and Allan E. Wulc, MD, FACS

Table 1. Patient-Reported Injection Pain With and Without Vibration Anesthesia

<table>
<thead>
<tr>
<th></th>
<th>With Vibration, No. (%)</th>
<th>Without Vibration, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pain</td>
<td>2 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Mild pain</td>
<td>35 (70%)</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Moderate pain</td>
<td>11 (22%)</td>
<td>22 (44%)</td>
</tr>
<tr>
<td>Severe pain</td>
<td>2 (4%)</td>
<td>17 (35%)</td>
</tr>
<tr>
<td>Worst pain ever</td>
<td>0 (0%)</td>
<td>5 (10%)</td>
</tr>
</tbody>
</table>

Figure 2. During treatment, the vibrating device was positioned on the patient’s skin, approximately 1 to 2 cm from the injection site.
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Treatment
Treatment
Treatment
Treatment

• Seeing a new provider? Previous Maps?
• Treatment onset?
• Duration of treatment efficacy?
• Which areas responded well to treatment?
• Any regions that did not respond well?
• Adverse effects?
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Antibodies
Impact of Botulinum Toxin Injections

Effects of Repeated Eyelid Injections with Botulinum Toxin A on Innervation of Treated Muscles in Patients with Blepharospasm


Rose M. Olson, B.S.¹, Ali Mokhtarzadeh, M.D.¹, Linda K. McLoon, Ph.D.¹,², and Andrew R. Harrison, M.D.¹,³

[Image of neuronal images labeled A and B, showing Neuromuscular Junction Density]
Impact of Botulinum Toxin Injections
Impact of Botulinum Toxin Injections

Modulating Neuromuscular Junction Density Changes in Botulinum Toxin–Treated Orbicularis Oculi Muscle

Andrew R. Harrison,^1,2 Zachary Berbos,^1 Renzo A. Zaldivar,^1 Brian C. Anderson,^1 Mollie Semmer,^1 Michael S. Lee,^1,5,4 and Linda K. McLoon^1,5

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Impact of Botulinum Toxin Injections

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Role of Zinc
Role of Zinc
Role of Zinc

Effect of dietary zinc and phytase supplementation on botulinum toxin treatments.

Koshy JC¹, Sharabi SE, Feldman EM, Hollier LH Jr, Patrinely JR, Soparkar CN

Purpose
To determine whether oral zinc supplementation might affect the efficacy and duration of botulinum toxin treatments.

Methods
In a double-blind, placebo-controlled, crossover pilot study, we examined the efficacy of three botulinum toxin preparations (onabotulinumtoxinA, abobotulinumtoxinA, and rimabotulinumtoxinB) following oral supplementation with zinc citrate 50 mg and phytase 3,000 PU, zinc gluconate 10 mg, or lactulose placebo in individuals treated for


Results
In seventy-seven patients, 92% of subjects supplemented with zinc 50 mg and phytase experienced an average increase in toxin effect duration of nearly 30% and 84% of participants reported a subjective increase in toxin effect, whereas no significant increase in duration or effect was reported by patients following supplementation with lactulose placebo or 10 mg of zinc gluconate. The dramatic impact of the zinc/phytase supplementation on some patients’ lives clinically unmasked the study and prompted an early termination.

Conclusions
This study suggests a potentially meaningful role for zinc and/or phytase supplementation in increasing the degree and duration of botulinum toxin effect in the treatment of cosmetic facial rhytids, benign essential blepharospasm, and hemifacial spasm.
Non-Pharmacologic Treatments

• Light Filter Lenses
• Eyelid Crutches
• External Magnetic Eyelid Device
• Transcranial Magnetic Stimulation
• Deep Brain Stimulation
Systemic Pharmacologic Treatments
Systemic Pharmacologic Treatment

• Dopamine Agonists
• Dopamine Inhibitors/Depleter
• Anticholinergics
• GABAergic
• Neural Membrane Stabilizing Agents
## Medical treatment of blepharospasm

Dhanya Vijayakumar\(^a\) and Joseph Jankovic\(^b\)

### Table 1. Pharmacotherapies in the treatment of blepharospasm.

<table>
<thead>
<tr>
<th>Pharmacological class</th>
<th>Mechanism of action</th>
<th>Pharmacological agent</th>
<th>Pertinent clinical use</th>
<th>Selected adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopaminergic agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine precursor</td>
<td>Dopamine precursor</td>
<td>Levodopa</td>
<td>- PD patients with blepharospasm as part of dystonic dyskinesia or wearing off dystonia</td>
<td>Nausea, drowsiness, orthostatic hypotension</td>
</tr>
<tr>
<td>Dopamine receptor</td>
<td>Dopamine receptor</td>
<td>Apomorphine</td>
<td>- Patients with blepharospasm as a symptom of atypical parkinsonian conditions</td>
<td>Nausea, drowsiness, sleep attacks, impulse control disorder, hallucination, injection-site reactions</td>
</tr>
<tr>
<td>agonist</td>
<td>agonist</td>
<td></td>
<td>- Dopa-responsive dystonia</td>
<td></td>
</tr>
<tr>
<td>Dopamine transporter</td>
<td>Blocks dopaminergic</td>
<td>Methylphenidate</td>
<td>- Patients with blepharospasm and increased daytime somnolence or fatigue secondary to use of other medications</td>
<td>Cardiac clearance needed due to risk of cardiac arrhythmia</td>
</tr>
<tr>
<td>blocker</td>
<td>reuptake into</td>
<td></td>
<td>- Patients with comorbid Attention deficit hyperactivity disorder (ADHD) (often co-existent in patients with Tourette syndrome)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>presynaptic terminals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticholinergics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GABA agonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GABA-A agonist</td>
<td>Trihexyphenidyl</td>
<td></td>
<td>- Younger patients with blepharospasm</td>
<td>Cognitive impairment in elderly</td>
</tr>
<tr>
<td>GABA-B agonist</td>
<td>Clonazepam</td>
<td></td>
<td>- Patients with multiple sites of dystonia like in generalized dystonic conditions</td>
<td>Drowsiness</td>
</tr>
<tr>
<td></td>
<td>Baclofen</td>
<td></td>
<td>- Most commonly used oral agent in blepharospasm patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Generalized dystonia/multiple dystonic sites</td>
<td>Drowsiness</td>
</tr>
</tbody>
</table>
# Medical treatment of blepharospasm

Dhanya Vijayakumar\textsuperscript{a} and Joseph Jankovic\textsuperscript{b}

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug</th>
<th>Indications</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neural membrane stabilizing agents</td>
<td>Carbamazepine</td>
<td>Use in conjunction with BoNT in patients with concomitant neuropathic pain symptoms as well</td>
<td>Hyponatremia, drowsiness</td>
</tr>
<tr>
<td></td>
<td>Mexiletine</td>
<td>Consider in patients with eyelid myotonia, or impaired eyelid relaxation</td>
<td>Sedation, ataxia, nausea</td>
</tr>
<tr>
<td></td>
<td>Lithium</td>
<td>Potential use in patients with comorbid mood symptoms that may benefit as well</td>
<td>Tremor, parkinsonism</td>
</tr>
<tr>
<td></td>
<td>Antihistamine</td>
<td>Potential consideration in patients with comorbid seasonal allergies</td>
<td>Drowsiness, fatigue</td>
</tr>
<tr>
<td></td>
<td>Cyproheptadine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local eyelid constrictors</td>
<td>Zolpidem</td>
<td>Consider in patients with insomnia</td>
<td>Sedation</td>
</tr>
<tr>
<td>Topical muscle relaxant</td>
<td>Apraclonidine</td>
<td>Short duration use in patients with premature wearing off of BoNT injection benefits</td>
<td>Local eye allergic reactions</td>
</tr>
<tr>
<td>Anti-androgenic drug</td>
<td>Topical acetyl hexapeptide-8</td>
<td>Concomitant use with BoNT with a trend to extend duration of benefit</td>
<td>Local skin allergic reactions</td>
</tr>
<tr>
<td></td>
<td>Finasteride</td>
<td>Single case report, insufficient data</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potential use in male patients with comorbid Benign prostatic hyperplasia (BPH)</td>
<td></td>
</tr>
</tbody>
</table>