Periorbital Applications of Botulinum Toxin
Is it Safe and Effective?

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UP College of Medicine – Philippine General Hospital

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Conflict of Interest

• None to declare
Outline

• History
• Mechanism, onset, and duration of action
• Formulation
• Preparation
• Reconstitution and storage
• Administration
• Functional applications of Botulinum Toxin
• Cosmetic applications of Botulinum Toxin
• Side effects and complications
• Immunogenicity
• Conclusion
2016 Survey of ASAPS
(American Society for Aesthetic Plastic Surgery)

- Americans spent a total of $13.5B
- 42% non-surgical procedures
- 4 Million Botulinum Toxin injections
  - Botox, Dysport and Xeomin
- 2 Million filler procedures
  - Restylane, Juvederm
  - Perlane, Belotero

www.surgery.org
BOTOX® Treatment Popularity

- **BOTOX® treatment**: 4.8 million
- **Laser hair removal**: 0.89 million
- **Soft Tissue Fillers**: 1.7 million
- **Microdermabrasion**: 0.91 million
- **Chemical peel**: 1.1 million

Number of cosmetic, minimally invasive procedures

Adapted from American Society of Plastic Surgeons Member Survey Data 2009.
Misconceptions with Botulinum Toxin

Typical Conversation with Clients

- But it’s a Toxin! That means it’s a poisonous!
- I’ve read / heard about this person who ....
- I thought you were (just) an Ophthalmologist...
- But its only temporary...
History of Botulinum toxin

1895
Prof Emile Pierre Marie van Ermengen identified *C. botulinum*

1946
Dr Edward Schantz isolated pure BoNT/A in crystalline form

1953
Dr Vernon Brooks showed that BoNT blocked the release of acetylcholine from motor nerve endings

1817-22
Dr Justinus Kerner published a complete description of food-borne botulism (sausage poison)

1980
Dr Alan Scott demonstrated the safety and efficacy of BoNT/A in humans (strabismus)

1989
Drs. Jean and Alistair Carruthers published the first paper on the use of BOTOX® for cosmetic purposes

2002
Allergan introduced BOTOX®, the first BoNT/A approved by US FDA for blepharospasm & strabismus

BOTOX® gained US FDA approval for glabellar lines
Botulinum Toxin (BTX)

- A powerful neurotoxin
- Produced by *Clostridium botulinum*, an anaerobic, Gram-positive, spore-forming bacillus
- Causes acute flaccid paralysis

BTX Serotypes

8 Serotypes: A, B, C1, C2, D, E, F, G

Antigenically and serologically distinct but structurally similar

A – most potent
A, B – used clinically
A, B, E – commonly associated with human botulism
Structure of Botulinum Toxin

- A simple dichain polypeptide that consists of a 100-kd “heavy” chain joined by a single disulfide bond to a 50-kd “light” chain

Images from: www.ebi.ac.uk
Normal Muscle Contraction

Nerve endings

Neuromuscular junction

Muscle cell

BTX inhibits the release of acetylcholine from peripheral nerve cells into neuromuscular junctions

Onset and Duration of Action

- The toxin requires **24-72 hours** to take effect
- Peak effect at about **10 days**
- Recovery of neuromuscular function at **3-4 months**

Formulations

**Botulinum Toxin A (BoNT/A)**
- OnabotulinumtoxinA (*BOTOX®*)
- AbobotulinumtoxinA (*DYSPORT®*)
- IncobotulinumtoxinA (*XEOMIN®*)
- Chinese botulinum toxin A (*CBTX-A*)
- Neuronox®
- Botulax®
- Nabota®
- Innotox®
- Topical BoNT/A (*Cosmetox®*)

**Botulinum Toxin A (BoNT/A)**
- RimabotulinumtoxinB (*MYOBLOC®*)
OnabotulinumtoxinA
BOTOX®, BOTOX® Cosmetic,
VISTABEL®, VISTABEX®
Allergan, Inc., Irvine, CA

• Preservative-free, vacuum-dried powder that contains 50 or 100 units (U) BoNT/A per vial + human albumin + NaCl
• Hall strain of C. botulinum type A
• US FDA-approved uses:
  • Blepharospasm, strabismus, overactive bladder, detrusor overactivity, chronic migraine, upper limb spasticity, lower limb spasticity, cervical dystonia, axillary hyperhidrosis
• Glabellar rhytides (frown lines), lateral canthal lines (crow’s feet)

Carruthers J, Carruthers A. Overview of botulinum toxin for cosmetic indications. In: UpToDate, Dover JS, Ofori AO (Eds), UpToDate, Waltham, MA, 2017.
AbobotulinumtoxinA
DYSPORT®,
AZZALURE®
Ipsen, Slough, UK/Galderma, Paris, France

• Contains 300 or 500 U of lyophilized abobotulinumtoxinA per vial + human albumin + lactose
• Hall strain of *C. botulinum* type A
• US FDA-approved uses:
  ➢ Cervical dystonia, upper limb spasticity, pediatric lower limb spasticity (≥ 2 years old), axillary hyperhidrosis
  ➢ Glabellar lines

Carruthers J, Carruthers A. Overview of botulinum toxin for cosmetic indications. In: UpToDate, Dover JS, Ofori AO (Eds), UpToDate, Waltham, MA, 2017.
IncobotulinumtoxinA
XEOMIN®, XEOMEEN®,
BOCOUTURE®, XEOMIN® COSMETIC
Merz Pharmaceuticals GmbH, Frankfurt, Germany

- Lyophilized powder that contains 50 or 100 U BoNT/A (Hall strain) + human albumin + sucrose
- Free of complexing proteins → reduces risk of sensitization and antibody formation against the toxin
- US FDA-approved uses:
  - Upper limb spasticity, cervical dystonia, blepharospasm previously treated with Botox®
  - Glabellar lines

Carruthers J, Carruthers A. Overview of botulinum toxin for cosmetic indications. In: UpToDate, Dover JS, Ofori AO (Eds), UpToDate, Waltham, MA, 2017.
Chinese Botulinum Toxin A
CBTX-A, BTXA™, PROSIGNE®, LANTOX®, REDUX®, LIFTOX®, LANZOX®, DITUROXAL®
Lanzhou Biological Products Institute, China

- 1 vial contains 100 U BoNT/A (Hall strain) + bovine gelatin + dextran + saccharose
- Approved for clinical use by the Ministry of Health in China since 1993
- An open, prospective, comparative trial comparing CBTX-A and BOTOX® in patients with blepharospasm and hemifacial spasm showed similar efficacy and safety profiles between the two drugs.
- Bovine gelatin may increase the risk of allergic reactions.

Images from Google
Korean Botulinum Toxin A
Neuronox®, Botulift®, Siax®,
Cunox®, Meditoxin®
Medytox Inc., Ochang, South Korea

• 1 vial contains 50, 100, or 200 U BoNT/A (Hall strain) + human albumin + NaCl
• Approved in 2006 by the Korean Food and Drug Administration
• Blepharospasm, equinus foot deformity due to spasticity in pediatric cerebral cerebral palsy patients ≥2 years of age, glabellar lines
Korean Botulinum Toxin A
Botulax®, Regenox®, Zentox®, Pegenox®, Reage®
Hugel Pharma, Seoul, Korea

- 1 vial contains 50, 100, 150 or 200 U BoNT/A + human albumin + NaCl
- Produced using the strain CBFC26
- Blepharospasm, equinus foot deformity, glabellar lines

www.hugel.ko.kr
Korean Botulinum Toxin A  
Nabota® , Evosyal®  
Daewoong Pharmaceutical, Seoul, Korea

• 1 vial contains 100 U BoNT/A + human albumin + NaCl
• Uses the KJ997761 strain
• Approved by the Korean FDA for glabellar lines in 2013
• Also for upper limb spasticity
Korean Botulinum Toxin A
Innotox®
Medytox Inc., Ochang, South Korea

- The world’s first liquid injectable form of BoNT/A
- Ready-to-use sterile liquid with 4 units/0.1 mL concentration (25 or 50 U/vial)
- Approved by the Korean FDA in 2013 for glabellar lines
- Uses *C. botulinum* type A Hall strain, similar to Botox® and Neuronox®
- Methionine and polysorbate as stabilizers
  - Avoids transmission of human blood-borne diseases

Topical Botulinum Toxin A (cream)  
Cosmetox®  
Transdermal Corp., Birmingham, Michigan

• Uses ionic nanoparticle technology (InPart), a transdermal noninvasive drug delivery technique preserves the bioactivity of molecules without denaturing them
• Intended for the softening of facial rhytides and a reduction in hyperhidrotic conditions

RimabotulinumtoxinB
MYOBLOC®, NEUROBLOC®
Solstice Neurosciences, LLC/Eisai Co., Ltd., Tokyo, Japan

- Supplied in liquid form in vials that contain 5000 U BoNT/B per mL + human albumin + sodium succinate + NaCl
- US FDA-approved use: cervical dystonia
- Less studied for cosmetic indications compared to BoNT/A

Carruthers J, Carruthers A. Overview of botulinum toxin for cosmetic indications. In: UpToDate, Dover JS, Ofori AO (Eds), UpToDate, Waltham, MA, 2017. Images from Google
Reconstitution of Botulinum Toxin A

Slowly inject the NaCl into the Botox vial.

Remove the syringe and gently mix the solution.

Attach a 1-cc syringe & aspirate required amount for injection.

Disconnect the 1 cc syringe and insert a 30G needle for injection.

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<table>
<thead>
<tr>
<th>Diluent* Added to 100 Unit Vial</th>
<th>Resulting Dose Units per 0.1 mL</th>
<th>Diluent* Added to 200 Unit Vial</th>
<th>Resulting Dose Units per 0.1 mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mL</td>
<td>10 Units</td>
<td>1 mL</td>
<td>20 Units</td>
</tr>
<tr>
<td>2 mL</td>
<td>5 Units</td>
<td>2 mL</td>
<td>10 Units</td>
</tr>
<tr>
<td>4 mL</td>
<td>2.5 Units</td>
<td>4 mL</td>
<td>5 Units</td>
</tr>
<tr>
<td>8 mL</td>
<td>1.25 Units</td>
<td>8 mL</td>
<td>2.5 Units</td>
</tr>
<tr>
<td>10 mL</td>
<td>1 Units</td>
<td>10 mL</td>
<td>2 Units</td>
</tr>
</tbody>
</table>

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Dilution Instructions for BOTOX® Cosmetic

Diluent Added
(Preservative-free 0.9% sodium chloride injection, USP only)

Resulting Dose (Units per 0.1 mL)

<table>
<thead>
<tr>
<th>100-Unit vial</th>
<th>2.50 mL</th>
<th>4.00 Units^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-Unit vial</td>
<td>1.25 mL</td>
<td>4.00 Units^a</td>
</tr>
</tbody>
</table>
Effect Of Dilution On Diffusion

2 U in 0.02 ml
5–7 mm
100 U in 1 ml saline

2 U in 0.05 ml
1.5 cm
100 U in 2.5 ml saline

2 U in 0.08 ml
2.5 cm
100 U in 4 ml saline

As determined by starch-iodine testing

Effect Of Dilution On Diffusion
The Ink Blot

Increasing Concentration of Botulinum Toxin
(Less diluent is added during reconstitution)

A more concentrated preparation causes greater weakening

Increasing Amount of Botulinum Toxin
(More Botulinum Toxin is injected into the treatment site)

Injecting more causes greater spread of the drug
FDA – Approved Uses of BOTOX®

- Blepharospasm
  - Benign Essential Blepharospasm
  - Blepharospasm associated with dystonia
- Facial nerve disorders (Hemifacial spasm)
Treatment Planning

- Observe twitching pattern at rest and on contracting the facial muscles
- Identify involved muscles based on facial movements
- Inject intramuscularly
Review Of Anatomy:
Muscles Of The Face

FRONTAL BELLY OF OCCIPITOFRONTALIS

- Raises eyebrows
- Wrinkles skin of forehead horizontally
Review Of Anatomy: Muscles Of The Face

ORBICULARIS OCULI

- Closes eyelid
Review Of Anatomy:  
Muscles Of The Face

ZYGOMATICUS MAJOR
• Elevates & abducts corner (angle) of mouth to smile
Review Of Anatomy:
Muscles Of The Face

RISORIUS

- Abducts angle of mouth, as in grimacing (draws angle of mouth laterally)
Review Of Anatomy:
Muscles Of The Face

MENTALIS

- Elevates and protrudes lower lip
- Pulls skin chin up, as in pouting
Review Of Anatomy:
Muscles Of The Face

ORBICULARIS ORIS

- Closes lips
- Puckers lips
Case 1: Blepharospasm

Orbicularis oculi
Case 2 - Blepharospasm

Procerus
Corrugators
Orbicularis oculi
Case 3: Hemifacial Spasm

Orbicularis oculi
Zygomaticus major
Case 4: Hemifacial Spasm

- Frontalis
- Orbicularis oculi
- Risorius
Botulinum Toxin - A

In 1989, FDA approved Botulinum toxin-A for treatment of:

- Strabismus
- Benign Essential Blepharospasm
- Facial Nerve Disorders Age ≥ 12 years
• 1990s – Canadian ophthalmologist Dr. Jean Carruthers observed the effect on crows feet around the eyes following BOTOX® treatment for blepharospasm

• Together with dermatologist husband Dr. Alastair Carruthers they have studied cosmetic indications of BOTOX®
Wrinkling Pattern In Aging

- The wrinkling pattern of the aging face follows naturally occurring creases, and are caused by habitual contraction of facial muscles.

- Facial lines are generally perpendicular to the orientation of the underlying muscle fibers.
# Treatment Planning

<table>
<thead>
<tr>
<th>MUST DO</th>
<th>MUST KNOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identify muscles to be treated</td>
<td>Knowledge of anatomy</td>
</tr>
<tr>
<td>Determine amount of Botulinum toxin-A to be used</td>
<td>Knowledge of drug dilution &amp; diffusion</td>
</tr>
<tr>
<td>Decide on treatment design</td>
<td>Requires judgment gained from experience</td>
</tr>
</tbody>
</table>
Cosmetic Applications To The Upper Face

REJUVENATION PROCEDURES (WRINKLE REMOVAL)
- Horizontal forehead lines
- Glabellar frown lines
- Crow’s feet
- Hypertrophic orbicularis oculi muscle (Orbicularis roll)
- Nasal scrunch (“bunny lines”)

FACIAL ENHANCEMENT & CONTOURING PROCEDURES
- Chemical brow lift
Cosmetic Applications To The Upper Face

REJUVENATION PROCEDURES (WRINKLE REMOVAL)
- Horizontal forehead lines
- Glabellar frown lines
- Crow’s feet
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- Nasal scrunch (“bunny lines”)

FACIAL ENHANCEMENT & CONTOURING PROCEDURES
- Chemical brow lift
The pattern of injection of the forehead varies, depending on the desired brow shape.
Horizontal Forehead Lines

PRE-INJECTION

POST-INJECTION
Note enhancement of brow to soft flare

Frontalis muscle

For females, a sharper V-shaped injection area creates a more arched brow
Injecting just the central portion of the frontalis muscle can leave residual wrinkles above the lateral eyebrow.
Horizontal Forehead Lines

PRE-INJECTION

POST-INJECTION

Frontalis muscle
Periorbital Complications of BTX

People with brow and lid ptosis try to compensate by constant contraction of the frontalis

Test for levator function!
Periorbital Complications of BTX

Decrease in vertical palpebral fissure after botulinum toxin injections to the horizontal forehead lines
Cosmetic Applications To The Upper Face

REJUVENATION PROCEDURES (WRINKLE REMOVAL)
- Horizontal forehead lines
- Glabellar frown lines
- Crow’s feet
- Hypertrophic orbicularis oculi muscle (Orbicularis roll)
- Nasal scrunch ("bunny lines")

FACIAL ENHANCEMENT & CONTOURING PROCEDURES
- Chemical brow lift
Glabellar Frown Lines

PRE-INJECTION

POST-INJECTION

Corrugator muscle

Horizontal fibers of the orbicularis oculi muscle

Procerus muscle
Glabellar Frown Lines

PRE-INJECTION

RELAXED

FROWNING

POST-INJECTION
Cosmetic Applications To The Upper Face

REJUVENATION PROCEDURES (WRINKLE REMOVAL)
- Horizontal forehead lines
- Glabellar frown lines
- **Crow’s feet**
- Hypertrophic orbicularis oculi muscle (Orbicularis roll)
- Nasal scrunch ("bunny lines")

FACIAL ENHANCEMENT & CONTOURING PROCEDURES
- Chemical brow lift
Crow’s Feet

Orbital portion (lateral portion) of the orbicularis oculi muscle
Cosmetic Applications To The Upper Face

REJUVENATION PROCEDURES (WRINKLE REMOVAL)
- Horizontal forehead lines
- Glabellar frown lines
- Crow’s feet
- Hypertrophic orbicularis oculi muscle (Orbicularis roll)
- Nasal scrunch ("bunny lines")

FACIAL ENHANCEMENT & CONTOURING PROCEDURES
- Chemical brow lift
Hypertrophic Orbicularis Oculi

ORBICULARIS ROLL

PROMINENT FAT PADS

ORBICULARIS OCULI MUSCLE

ORBITAL PORTION

PALPEBRAL PORTION

Pre-tarsal orbicularis oculi
Pre-septal orbicularis oculi
Hypertrophic Orbicularis Oculi

GOALS OF TREATMENT

- Soften hypertrophic muscle “bulge”
- Widen vertical palpabral fissure
Hypertrophic Orbicularis Oculi

Widening of the vertical palpebral fissure post-injection in both relaxed & smiling
Cosmetic Applications To The Upper Face

REJUVENATION PROCEDURES (WRINKLE REMOVAL)
- Horizontal forehead lines
- Glabellar frown lines
- Crow’s feet
- Hypertrophic orbicularis oculi muscle (Orbicularis roll)
- **Nasal scrunch (“bunny lines”)**

FACIAL ENHANCEMENT & CONTOURING PROCEDURES
- Chemical brow lift
Nasal Scrunch Or “Bunny Lines”

Nasalis muscle

Contraction causes “wolf lines” that run from medial canthus to nasal bridge

2 to 4 units & massage
Cosmetic Applications To The Upper Face

REJUVENATION PROCEDURES (WRINKLE REMOVAL)
- Horizontal forehead lines
- Glabellar frown lines
- Crow’s feet
- Hypertrophic orbicularis oculi muscle (Orbicularis roll)
- Nasal scrunch (“bunny lines”)

FACIAL ENHANCEMENT & CONTOURING PROCEDURES
- Chemical brow lift
Chemical Brow Lift

Chemical brow lift is more an enhancement than a rejuvenation (wrinkle removal) procedure.
Impact Of Brow Shape

**Classic** - Artistic, Romantic
This eyebrow shape is always in fashion, compatible with all make-up styles.

**Arch** - Confident, Dynamic
May appear a little aloof, while still giving the image of sensuality

**Flat** - Innocent
Pure, sincere, impulsive

**Round** - Resourceful, Cheerful
An entertainer, happy-go-lucky

Sign from Shu Uemura cosmetic store in Singapore, Feb 2000
The £20m business of brows

Kathleen Baird-Murray
May 6, 2016
# Brow Elevators & Depressors

<table>
<thead>
<tr>
<th>MUSCLE</th>
<th>ACTION ON THE BROW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontalis muscle</td>
<td>Elevator</td>
</tr>
<tr>
<td>Corrugator muscle</td>
<td>Adductor</td>
</tr>
<tr>
<td>Procerus muscle</td>
<td>Depressor</td>
</tr>
<tr>
<td>Orbicularis oculi muscle</td>
<td>Adductor &amp; depressor</td>
</tr>
</tbody>
</table>
The Arched Brow

Orbital portion of the orbicularis oculi muscle

Corrugator muscle

Procerus muscle
The Flared Brow

Orbital portion of the orbicularis oculi muscle
The Horizontal Brow

Orbital portion of the orbicularis oculi muscle

Procerus muscle
Brow Reshaping

Round brow
Pre-treatment

Arched brow
Depression of medial brow due to unopposed procerus action after treatment of medial frontalis
Should I have Botulinum toxin injected on me?
85 patients (19 to 79 years of age) with glabellar frown lines were treated with reconstituted BOTOX® for periods of time ranging from 1 day to 6 weeks.

Muscle motility and presence of wrinkles were evaluated up to 60 days post-treatment.

BOTOX® may be applied up to 6 weeks after reconstitution without losing its effectiveness.
Side Effects and Complications

Botulinum toxin is relatively safe and well-tolerated with the following:

**APPROPRIATE PATIENT SELECTION**

**PROPER DOSING**

**INJECTION TECHNIQUES**

Side effects are usually mild and transient and most commonly include swelling or bruising at the injection site, mild headache, or flu-like symptoms.
Side Effects and Complications

No confirmed serious case of spread of Botulinum toxin effect away from injection site

**Spread of Toxin Effect**
- Asthenia
- Generalized muscle weakness
- Diplopia
- Ptosis
- Dysphagia
- Dysphonia
- Dysarthria
- Urinary incontinence
- Breathing difficulties

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Kim Kardashian’s Botox bruises after injection around the eyes

Drooping of upper lids Botox injection around the eyes

BOTOX® Product Information
Immunogenicity

11/2,240 subjects (0.49%) exhibited seroconversion
3 subjects became clinically unresponsive to onabotulinumtoxinA

Botox contains a protein product that can elicit antibody formation

The presence of neutralizing antibodies does not always predict non-response to Botox treatment
Immunogenicity

Botulinum Toxin

P K Nigam and Anjana Nigam

Risk Factors:

• Injection of >200 units per session
• Repeat or booster injections given within 1 month of treatment

Injecting the lowest effective doses, with the longest feasible intervals between injections, may minimize the risk for immunogenicity

_**IncobotulinumtoxinA**’s immunogenicity may be different from OnabotulinumtoxinA and AbobotulinumtoxinA that of since it is free from complexing proteins_

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Conclusion

- Botulinum toxin A is safe and effective in treating involuntary muscle action of Blepharospasm & Hemifacial spasm
- Botulinum toxin A is safe and effective in achieving facial rejuvenation and enhancement
- A thorough understanding of facial anatomy and injection techniques, as well as proper dilution and storage, are essential to a successful outcome without complications.
Thank you for your attention!

15 – 21 December 2017
See you in Manila!