The effect of topical botulinum toxin eyedrop on palpebral fissure height, ocular surface and tearing

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1) **Protocol Title**

The effect of topical botulinum toxin eyedrop on palpebral fissure height, ocular surface and tearing.

2) **Objectives**

Aim 1: To determine the effect of botulinum toxin eyedrop on palpebral fissure height.

Aim 2: To determine the effect of botulinum toxin eyedrop on ocular surface.

Aim 3: To determine the effect of botulinum toxin eyedrop on tearing of the eye.

Hypothesis: We hypothesize that the application of a botulinum toxin (BT) eyedrop will cause a decrease in subjects' palpebral fissure height, improve ocular surface disease, and decrease reflexive tearing in patients with dry eyes.

3) **Background**

BT is a neurotoxin produced by the bacterium Clostridium botulinum and related species. (1) It prevents release of acetylcholine, a neurotransmitter from axons ending at the neuromuscular junction, causing paralysis.(2) Dr. Alan B. Scott used the first documented therapeutic application of BT when he used it for strabismus by injecting it into the extraocular muscles.(4) In 1989, BT was licensed by the U.S. Food and Drug Administration for treatment of strabismus.(4) Since then, there has been massive research on BT, which has led to the addition of newer formulations with a large range of indications. To date, BT has been widely used by neurologists and cosmetic practitioners. Recently, urologists and pain specialists are increasingly using BT for various indications. Nevertheless, neurological disorders are the most common therapeutic indication of BT. (5)

The seven main types of BT are type A to G (A, B, C1, C2, D, E, F and G).(6) Types A and B can cause disease in humans but are also used for therapeutic and cosmetic etiologies.(7) The effect of BT-A on shaping the eyebrow was first reported in 1989.(8) BT injections for facial wrinkles is the most frequently performed cosmetic procedure in the United States. BT is used for the treatment of frown lines, forehead lines, and crow's feet, which are the cosmetic indications approved by the FDA. (9)

BT has a broad margin of safety (lethal dose 50% (LD50)) in humans that can reach up to 40 U/kg BW. Therefore, its cosmetic use is relatively safe. BT does not cause any long-term adverse or side effects or persistent changes at the nerve terminals and targeted muscles. (10) Some known adverse effects for BT injection use include eyelid ptosis and weakness of the muscles. Rare complications of BT injection use include dysphagia, botulism, and possibly death, usually seen in patients treated for non-cosmetic issues. (11)

Graves' ophthalmopathy (GO) or thyroid eye disease is a potentially sight-threatening ocular disease that has puzzled physicians and scientists for nearly two centuries, usually occurring in patients with hyperthyroidism or a history of hyperthyroidism.(12) The most common clinical sign of GO is upper eyelid retraction, occurring to a various extent in about 90% of the patients suffering from GO.(13) It may cause cosmetic complaints as well as functional problems due to, for example, exposure keratitis.

Surgical correction may be performed because of corneal exposure at any time during the disease, cosmetic rehabilitation usually after the disease is inactive and after other interventions such as orbital decompression or strabismus surgery are done. (14) During the active phase of the disease, it's better not to do any surgery, although patients with severe lid retraction may suffer from keratitis during this long period of exposure. Some alternatives for surgery to treat thyroid lid retraction have been postulated, such as, local guanethidine, but it was not used due to adverse side effects.(15) In another study, somatostatin or prednisolone were used for eyelid retraction; however, there was little effect in the palpebral fissure height.(16) Several reports illustrated the effects of injections with BT in thyroid lid retraction; (17-20) In some studies BT injection was done through the skin with 5-6 units in the eyelid (21, 22). In other studies injections were done through the conjunctiva with upper eyelid eversion (23, 24) with up to 10 units of BT. Some adverse effects of BT injections are entropion, ectropion, epiphora, photophobia, diplopia and ecchymosis. (25)

The purpose of this study is to see simply if eyelid position changes with a drop of BT in the eye, removing the stress and discomfort of any injections, especially important in non-cooperative patients since there have been no studies of such kind.

BT injection into the lacrimal gland has been also used to treat epiphora in patients with aberrant regeneration after 7th nerve palsy leading to crocodile tears. (26, 27). The effects of topical BT have not been studied on tear production. In our study we will use Schirmer's I test with topical anesthesia and tear meniscus height (27) to see the effect on tear production at different intervals. Also tear break up time (TBUT) and corneal fluorescein staining will be used to evaluate the ocular surface.

4) **Inclusion and Exclusion Criteria***

Inclusion Criteria

- Adults aged 18 and above that present to the oculoplastic and reconstructive surgery department that are able to provide informed consent to participate
- Presence of upper eyelid retraction or asymmetry(>1mm)

Exclusion Criteria

- Adults unable to consent
- Individuals less than 18 years of age
- Prisoners
- Pregnant women.
    - Patients will be asked if they are pregnant by research staff before participation in the study.

  Women who are breast-feeding
- Known contradictions or sensitivities to study medication
- Grossly abnormal lid margins, anatomical abnormalities
- Variable ptosis or eyelid position (e.g., myasthenia gravis, blepharospasm)
- Any ocular or systemic condition that, in the opinion of the investigator, would confound study data, interfere with the subject's study participation, or affected the subject's safety or trial parameters
- Presence of an active ocular infection
- Inability to sit comfortably for 15 – 30 minutes
- Botulinum toxin injection in the eyelids during the past 3 weeks.
- Neuromuscular disorders (e.g., Parkinson's disease or myasthenia gravis)
- Medication use known to interfere with the effects of BTX-A within the previous 1 month (e.g., aminoglycoside or benzodiazepines),
- Previous history of hypersensitivity reactions to BTX-A
- Dysfunction of tear production or secretion (e.g., meibomian gland dysfunction or Sjogren's syndrome),

5) **Procedures Involved***

Patients coming to the oculoplastic clinic who qualify for the study based on inclusion and exclusion criteria (With upper lid retraction or asymmetry>1mm) will have the study explained to them by a research study member and they can ask questions. They will receive information on risks and benefits to research participation. For interim analysis of futility, we will do the study with BT eye drops on first 10 patients and then evaluate the results to see if there are any significant effects. If clinically significant effects are seen, then 34 patients totally (17 in BT vs 17 in saline) are included. After a written consent is obtained, External Photographs will be taken by a standard camera in standardized room light. Eyelid measurements will be done including MRD1, MRD2, PF height with the eyes in the primary position. Tear meniscus height, Schirmer I test with anesthesia and ocular staining with fluorescein will be evaluated for all patients recruited before and after eye drops are installed by the PI or resident in the clinic in the eye with greater palpebral fissure heigh (one eye). In each visit all these data will be obtained again. The subjects will be allocated to the treatment based on the randomization sheet provided by the biostatics department that is handed to Solia Rodriguez, Surgical Coordinator on the 4th who will inform the PI of the patient's number. After the PI see's the patient, she will inform the resident in the clinic. The resident or the fellow in the clinic will be asked to provide the PI with the eye drop (botulinum toxin A or saline in 1 cc syringes without needles) while not informing of the contents. The research team(Shanlee Stevens, Marissa Shoji, Zahra Markatia, Kambiz Ameli), also blinded to the study will gather the data and take the necessary photos (double Blinded).

Potential toxicity or life-threatening toxicity with topical botulinum toxin is unlikely.

Pressure on the lacrimal sac by the patients for 2 minutes will be done to minimize systemic absorption.

Patients will be provided a phone number to call if any complications occur.

BOTOX®, JEUVEAU, XEOMIN, and DYSPORT are Crystalline preparations of BT type A, FDA approved drugs for many indications including periocular wrinkles. Saline eye drops will be also used as placebo.

If any patient develops side effects that require a medical need to unblind and treat, the PI can find out which group was the patient allocated (unblinding) by contacting solia rodrigeuz.

Number of Subjects

10 Patient are recruited for interim analysis of futility. If significant, then 17 patients in each group (34 total) based on power calculations for alpha of 0.05 and power of 80% per the biostatistics department.

Study Timelines

Recruitment will occur for 1 year. After interim analysis, the study will end once 34 patients are recruited. The study length for the patient is expected to be at least 3 months, with the recruitment/baseline visit and follow up visits at 3 days, 1 week, 2 weeks, 1 and 3 months from the first visit, for a total of 6 visits. The study is expected to last about 1 year from the time of IRB approval to completion of all study activities, including analysis of identifiable data.

Botulinum Toxin Drug Product

Botulinum toxin under the names BOTOX, JEUVEAU, XEOMIN, and DYSPORT, is an FDA approved drug for the treatment of Moderate to severe glabellar lines, moderate to severe lateral canthal lines, known as crow's feet, strabismus, blepharospasm, neurogenic detrusor overactivity and chronic migraine.

It is a crystalline preparation of BT type A. This agent should be considered exempt from IND requirements as it meets the below IND criteria.

The research is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug.

The research is not intended to support a significant change in the advertising for the product.

The research does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

The research is conducted in compliance with the marketing limitations described in 21 CFR §312.7.

Drug insert is available and attached to the IRB protocol.

Procedures Involved

We anticipate that the procedures listed below will take about 30 to 40 minutes per patient. Each patient will have a complete ophthalmologic exam. Except as noted, the procedures below are not considered standard of care and are being conducted for the study alone.

A. Part 1: Pre-treatment data collection
    - External photographs, MRD1, MRD2, palpebral fissure height, tear meniscus height, Schirmer I test with anesthesia and ocular staining with fluorescein will be recorded.
B. Part 2: Botulinum toxin or Placebo topical application
    - Subjects will be randomized to receive either 15 units of botulinum toxin A (BOTOX), incobotulinum toxin A (XEOMIN), prabotulinum toxin A (JEUVEA), the equivalent of 45 units of abobotulinum toxin A (DYSPORT) or balanced saline placebo in one eye after 10 patients are included for the interim analysis with BT eye drops topically on the surface of the eye
    - Then based on the randomization results, the examiner will apply botulinum eye drops or saline to the one of the subject's eyes.
C. Part 3: Post-treatment data collection
    - Subjects will come back in 3 days, 1 week, 2 weeks, 1 & 3 months after they receive the treatment or control.
    - At each visit, subjects will have the measurements above again.
D. Part 4: Data analysis
    - Data will be recorded and stored in a secure Microsoft Office Excel (Microsoft Corporation, Redmond, WA, U.S.A.) spreadsheet. Data will be graphically analyzed and represented with Adobe Photoshop (Adobe, Inc., San Jose, CA, U.S.A).
    - Data assessed will involve assessing pre- and post-treatment MRD1 and MRD2, investigator-assessed measurements of ocular surface and tearing.
    - User performing analysis will be blinded to which eye received study drug.

Follow-up outside of the patient's next routine clinic visit will be needed for 3 days, 1 week, 2 weeks and 1 & 3 months. Patients who do have symptoms concerning any post-procedural complications will be instructed to notify study staff immediately. A phone number will be provided.

Outcomes Measurs:

Primary outcome:

Outcome Measure Title: Change in palpebral fissure height

Outcome Measure Description: Palpebral fissure height will be calculated from the sum of marginal reflex distance 1 and 2 measured by the researcher.

Outcome Measure Timeframe: Baseline, day 3, 7,14, 30 & day 90.

Secondary outcomes:

Outcome Measure Title: Change in eye ocular surface and tearing

Outcome Measure Description: Scoring of ocular surface and tearing will be done by fluorescein staining with a slit lamp and Schirmer I test with anesthesia.

Adverse Events and Serious Adverse Events

Treatment-emergent adverse events, defined as any event, not present prior to the initiation of the drug treatment or any event already present that worsens in either intensity or frequency following exposure to the drug treatment, will be monitored and reported throughout the study. Treatment emergent adverse scale will be graded as the following:

- Mild: Transient or mild discomfort (<48 hours) to the subject; no medical intervention/therapy required.

- Moderate: Mild to moderate limitation in activity of the subject; no or minimal medical intervention/therapy required.

- Severe: Marked limitation in activity of the subject, some assistance usually required; medical intervention/therapy required including possible hospitalization.

Serious adverse events are defined as those which result in death, hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (aka disability), or congenital anomaly / birth defect.

Previously reported treatment-emergent adverse effects are described further in the risks section below.

Withdrawal of Subjects

Patients may withdraw at any time at their discretion. Subject withdrawn from and/or terminated from research with or without their consent are those who are found to not meet inclusion/exclusion criteria, and/or are not able to complete the research protocol in its entirety, as well as those who suffer a treatment-emergent adverse effect requiring medication discontinuation. For any subjects who withdraw from research, including partial withdrawal from procedures, study data of the withdrawn subject will not be included in statistical analysis and will be shredded.

Data Analysis

Statistical analysis will be performed by the Oculoplastic Research Laboratory research fellow. A paired t-test will be used to analyze the difference in palpebral fissure height, ocular surface and tearing. 34 subjects will be required to perform perimetric statistics.

6) **Risks to Subjects***

The primary risks to the subjects are adverse reactions to the medication. These risks are explained to patients prior to their arrival to the oculoplastic clinic. Previously described potential adverse reactions when injecting the periocular area are dull and transient headaches with malaise, Ptosis. Severe reactions seen in injections of BT in non-periocular areas such as anaphylaxis, soft-tissue edema and dyspnea are rare in occurrence. (28) Injection of BT in neck: Hoarseness and dysphagia). (28)

All are reversible side effects. (28)

Subjects may have mild ptosis in due to botulinum eye drop but it will eventually improve. Also, the drop can be used in the opposite eye to give symmetry.

Potential psychosocial risks to subjects include time taken from their day to undergo tests, potentially missing work, and anxiety or discomfort from the eye drop instillation process. This study is not collecting sensitive information, thus no potential risk to reputation or legal risks should occur.

Subjects will be instructed to call immediately for an appointment if they notice a change in their vision, eye redness, or the development of pain in either eye. Care will be taken by all study members to prevent the occurrence of any adverse events.

There are no well-controlled studies of BT-A eye drops in pregnant women, and the risks to the fetus or embryo are unknown/unforeseen. One prior publication reported abortion or fetal malformations which have been observed in rabbits after injection (29) however, another larger prospective study found no increased risk of malformations associate with BT-A for chronic migraine during pregnancy in 45 patients (30). No studies have been performed evaluating topical BT ophthalmic solution. BT is classified as US FDA pregnancy category C. (29)

- US FDA pregnancy category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Participants will be informed of the above information and reserve the right to decline participation in the study. We will not be following pregnancy outcomes.

Unanticipated problems or complications will be reported to the IRB according to posted guidelines.

Risks of the study are listed above and will be minimized by the following:

- Study will be discontinued if subjects experience any negative effect from the medication
- Patients with a known sensitivity or history of adverse reaction to BT or similar medications will be excluded from the study

As with any study, there is a risk of confidentiality breach. The research members will assign each patient a specific ID number and place this information on a separate spreadsheet. No names will be used in the forms. Presentations and publications will not identify individual patients.

7) **Potential Benefits to Subjects***

There will be no direct benefit to patients participating in the study. Their involvement may provide satisfaction for aiding in future research, particularly if they would be interested in personally using the agent to decrease their own palpebral fissure height.

8) **Vulnerable Populations***

None, not applicable

9) **Setting**

Study location will be at the Oculoplastic clinic.

10) **Resources Available**

Principal investigator will be in charge of the studies and has been involved in multiple human clinical trials at the University of Miami.

Resident physicians have extensive experience in clinical research, slit lamp examination and data collection and analysis.

11) **Prior Approvals**

None.

Recruitment Methods

The principal investigator of this study will assess patients for study eligibility by reviewing the medical record. These patients will be coming in during their normal visit at the Oculoplastic Clinic. They will ask eligible patients if they are interested in hearing about the study. No phone calls for recruitment will be made prior to the regular clinic visit. No payment will be provided to patients for their participation.

12) **Consent Process**

After identifying eligible study subjects, those who are interested in participating will be given a scheduled appointment to meet with research staff to review the consent form. The consent process will take place in Oculoplastic Clinic. Adequate time will be devoted to the consent discussion; the patients will be given ample time to review the consent form and ask questions. If patients have a different language than English, such as Spanish as their native language, a translator will be used to explain the research process. A separate consent translated in that appropriate language will be created prior to signing the consent. A witness will be used if the patient has vision impairment and is unable to read the consent.

13) **Process to Document Consent in Writing**

Consent of the subject will be documented in writing.

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