Title: Randomized, Single Center, Masked Study Comparing the Efficacy of Botulinum Toxin Type A Injection After Topical Anesthesia versus Petrolatum Ointment

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Title: Randomized, Single Center, Masked Study Comparing the Efficacy of Botulinum Toxin Type A Injection After Topical Anesthesia versus Petrolatum Ointment

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Population: Sample size ~14, male/female, 18 – 65 years of age, diagnosed with forehead rhytides electing for treatment with botulinum toxin Type A

Number of sites: 1, Robert Cizik Eye Center

Study Duration: Patient participation time will be approximately 16 weeks

Background:

Botulinum toxin type A (BTX-A) is a potent neurotoxin that blocks the presynaptic acetylcholine release at the neuromuscular junction, causing a dose-dependent weakness or paralysis of skeletal muscle. Recovery of muscle function occurs through proximal axonal sprouting and muscle re-innervation by formation of a new neuromuscular junction. Botulinum toxins are currently used for the treatment of a variety of medical disorders including spastic facial conditions (essential blepharospasms, hemifacial spasms), strabismus, sphincter dysfunction, hyperlacrimation, hyperhydrosis and headaches (1-4). In addition, botulinum toxin has been used in the treatment of facial rhytides such as crow's feet, and glabellar lines with great aesthetic results (5, 6). More recently, the US Food and Drug Administration approved the use of Botox for the temporary improvement in the appearance of moderate to severe forehead lines associated with frontalis muscle activity in adults.

A number of factors have been postulated that may affect the efficacy and duration of action of botulinum toxin type A including reconstitution process, dilution (units per volume), storage time after reconstitution and depth of administration (7,8). The use of topical anesthetic prior to administration of BTX-A for the treatment of facial cosmetic rythides and blepharospasm has been proposed to have a deleterious impact on BTX-A effect, but the data is very limited (7). Multiple studies have investigated the use of

topical vibration, topical ice, vapocoolants and topical anesthesia as methods to decrease the pain associated with the injection of BTX-A (9-12) without decreasing the efficacy of BTX-A. However, there is no consensus on standard of care for administration of anesthesia prior to BTX-A administration. While many surgeons use one or a combination of the anesthetizing methods above to decrease pain associated with the injection, others use none.

OBJECTIVES

The objective of this study is to determine whether there is a difference in clinical effect (weakness/paralysis of the frontalis muscle), duration of effect, level of discomfort and patient satisfaction in patients receiving topical anesthesia (2.5% lidocaine/2.5 % prilocaine cream, Impax Laboratories, LLC) on one side of the forehead and petrolatum ointment on the other prior to BTX-A administration for the treatment of forehead rhytides.

Outcome Variables

- Primary outcome variable is change of eyebrow excursion on each side of the forehead from baseline to each follow-up visit.

- Secondary outcome variables
    - Duration of effect, defined as the elapsed time from injection to the end of botulinum, such that return of baseline frontalis function, i.e. within 2 mm of baseline value
    - Perception of pain immediately after injection at each side
    - Patient satisfaction for each side
    - Patient's perception of difference in efficacy

STUDY DESIGN

This is a prospective, randomized, double-masked, comparative study in patients who present at the Robert Cizik Eye Clinic with horizontal forehead rhytides requiring treatment with botulinum toxin Type A (Botox ®; Allergan, Irvine, CA, USA).

PARTICIPANTS

All patients who meet the following eligibility criteria may be enrolled.

Inclusion criteria

Patients who meet the following inclusion criteria may be enrolled:

- Subjects 18 to 65 years of age
- Presence of horizontal forehead rhytides
- Good eyebrow excursion (≥5 mm)
- Able to understand and sign an informed consent form that has been approved by the Committee for Protection of Human Subjects

Exclusion criteria

Patients who meet the following exclusion criteria may NOT be enrolled

- Previous injection of botulinum toxin in the intended treatment area for the study within the last 4 months
- Known allergy to botulinum toxin
- Known history of sensitivity to local anesthetics of the amide type
- Existing disorder of neuromuscular transmission (e.g. Myasthenia gravis or Lambert-Eaton syndrome)
- Usage of medication with effect on neuromuscular function
- Women of childbearing potential (who are not postmenopausal for at least 1 year or surgically sterile), who are pregnant or nursing or intend to become pregnant during the time of the study
- Significant brow asymmetry (> 5mm)
- Unable to follow-up for the duration of the study (16 weeks)

STUDY DESIGN CONSIDERATIONS

Randomization

A computer-generated randomization table will be used to assign which side of the forehead receives topical anesthetic and which side receives 41% petrolatum jelly (placebo) prior to the BTX-A for each participant.

Masking

The randomization information will only be known by the principal investigator performing the injections and will not be disclosed to the participants or the brow excursion examiner.

Sample Size Calculations

This study is design to compare change of eyebrow excursion from baseline at each side of forehead. Tzou (2005) reported that the standard deviation of eyebrow excursion was 2.31 mm in both European and Asian populations (16). To detect a 2 mm differences between 2 sides, a sample size of 14 is required to have 5% significance level and 90% power.

Recruitment period

Recruitment for this study is anticipated to take approximately 4-6 weeks.

RECRUITMENT PROCEDURE

All patients who meet eligibility criteria electing to undergo treatment with BTX-A will be offered this study. All patients interested will be provided with a written consent. Those who agree to participate, informed consent will be obtained and the participant will proceed into the Baseline Exam.

Randomization Procedure

Upon completion of the Baseline Visit and eligibility of the participant is confirmed, their randomization assignment will be obtained from the computer-generated randomization table.

TREATMENT

For each patient, one half of the forehead, divided from the contralateral side by an imaginary vertical line through the dorsum of the nose, will be treated with a thick layer of topical 2.5% lidocaine/2.5 % prilocaine cream (Impax Laboratories, LLC), while the other will be treated with 41% petrolatum ointment. After, 30 minutes, the ointment will be wiped away and the forehead will be cleaned with an alcohol swab and allowed to. Botulinum toxin type A (Botox, Allergan Pharmaceutical, Irine, CA, USA) vials will be reconstituted with 0.9 % NaCl bacteriostatic solution by adding 2 ml to 100 units of lyophilized toxin. A 1cc syringe with a 30-gauge 1/2-inch needle will be used to administer at each site (1 syringe- needle for each side). Two units of BTX-A will be administered at each injection site. There will be 5 injection sites per side of forehead, for a total of 10 injection sites (20 units) for each participant. All injections will remain at least 2 cm from the superior orbital rim to reduce the potential of brow and eyelid ptosis.

If there is toxin remaining in the vial, this will be stored/refrigerated until needed again. Before it is used, the cap will be cleaned off with an alcohol swab. If an open, reconstituted vial is not used after 48-72 hours, the toxin will be discarded (13).

Participant perception of pain at the injection site will be evaluated by asking them to rate their pain, on a scale 0-10 for each side of the forehead (see Appendix 1).

SCHEDULED STUDY VISITS AND ASSESSMENTS

Baseline Visit

After reviewing and signing the informed consent form, all potential participants will undergo a baseline evaluation in order to determine study eligibility, establish baseline ocular characteristics and determine randomization group based on the computer-generated assignment. Participant demographics including age, gender, and race will be recorded as well as medical and medication history which will include previous use of botulinum toxin and if so the location of the injection and the date.

Scheduled Follow-up Visits

Participants will follow-up 2 weeks (+/- 3 days), 6 weeks (+/- 2 weeks) and 16 weeks (+/- 2 weeks) after the injection.

Table 1. Time Windows for Scheduled Follow-up Visits (number of days after injections)

Follow-Up Visit	Ideal Follow-up Time	Visit Window
Week 2	14 days	11 days – 17 days
Week 6	42 days	35 days – 49 days
Week 16	112 days	98 days – 126 days

Scheduled Assessments

Table 2 outlines the schedule of assessments at each visit throughout the study period.

Table 2: Schedule of Assessments

Assessment	Baseline	Injection	Week 2	Week 6	Week 16
Informed Consent	X				
Demographics	X				
Medical/Ophthalmic History	X				
Medication History	X		X	X	X
Inclusion/Exclusion Criteria	X				
Exophthalmometry	X		X	X	X
Bilateral Brow Excursion	X		X	X	X
External Photography-relaxed neutral expression	X		X	X	X
External Photography-maximal brow elevation	X		X	X	X
Injection		X			
Satisfaction Survey			X	X	X

Universal Pain Scale		X			
Randomization	X				
Adverse Events		X	X	X	X

Assessments

The same examiner should perform the same assessments for each participant.

Medications

All current patient medications, including vitamins and supplements should be documented and reviewed, to assess for any medication that may affect neuromuscular function at all study visit.

Exophthalmometry

The distance between both lateral canthi will be measured using a Hertel exophthalmometer (mm) at Baseline, Week 2, Week 6 and Week 16 Visits.

Brow Excursion

Brow excursion will be assessed at Baseline, Week 2, Week 6 and Week 16. Visits. Examinations will be performed by a masked examiner. Eyebrow excursion will be measured by using a purple marking pen and placing a mark just above the brow, parallel to the center of the pupil while the participants is in a relaxed neutral expression. Then, the participant will then be asked to raise the brows and the excursion of the brow from resting position to maximum elevation will be measured in millimeters.

External Photography

Patients will be photographed at Baseline, Week 2, Week 6, and Week 16 Visits. Photos will be taken using the same digital camera. Patients will be photographed in both a relaxed, neutral expression, and while exhibiting maximal voluntary eyebrow elevation. All photos will be transferred to Adobe Photoshop (Adobe Systems, INC).

The method described previously by Gordin EA et al. (8) will be used to assess eyebrow height. The lateral intercanthal distance will be measured to standardize the photos by drawing a horizontal line from one lateral canthus to the other. Baseline brow height will be obtained measuring the distance between the line and a point taken at the superior-most aspect of the eyebrow, positioned directly above the mid-pupillary axis. Measurements will be made at 150% magnification, viewing images on and Mac OS High Sierra Version 10.13.3 with a 15-in display and a screen resolution of 1920 x 1200 pixels. The lateral intercanthal distance will be used to normalize the brow eight from each photograph to account for any differences in the camera-to-patient distance. For each patient, the ratio brow height to intercanthal distance will be calculated. Then the ratio obtained during the neutral brow position will be subtracted from that measure during active brow elevation for both sides (pretreatment with anesthetic and petrolatum) to yield brow elevation. This will be calculated for each picture taken at the baseline visit and at each follow up visit.

Participant Appearance Satisfaction Survey

Participant satisfaction survey will be conducted at Week 2, Week 6 and Week 16 Visits. The survey will include questions about the overall appearance of their forehead for each side and will be recorded using a 5-point rating scale: 4 = very satisfied, 3 = satisfied, 2 = neutral, 1 = dissatisfied and 0 = very dissatisfied. Participants will also be asked if there is a noticeable difference between the 2 sides of their face.

Universal Pain Scale Assessment

Participant pain and/or discomfort will be assessed on the day of Injection (post injection) (Appendix 1) for each side.

ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a participant who is administered a test article. The AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including

an abnormal laboratory finding), symptom, or disease temporally associated with study treatments.

A non-serious AE is defined as a change in a participant's ophthalmic and/or medical health that is not life-threatening, does not require hospitalization, does not prolong a current hospitalization and is not disabling. All AEs must be reported whether they are considered study-related or not.

Serious Adverse Events

A serious adverse event is defined as any adverse experience occurring at any time during the study that results in:

- Death
- Life-threatening
- Inpatient hospitalization
- Prolongation of existing hospitalization
- Disability or permanent damage (including vision threatening complications)
- A congenital anomaly/birth defect
- Required intervention to prevent permanent impairment or damage and/or other serious important medical events

All SAEs will be submitted to the IRB pursuant to their IRB policy.

Recording Instructions

Mild, moderate, or severe should be used to describe the maximum intensity of the adverse event.

- Mild – Does not interfere with the participant's usual functions
- Moderate – Interferes to some extent with the participant's usual functions
- Severe – Interferes significantly with the participant's usual functions

It should be noted that a severe intensity does not necessarily mean it is an SAE.

The investigator will also be asked to determine the likelihood of the relationship between the study intervention and the AE.

Follow-up of Adverse Events

For participants who have ongoing ocular adverse events at the time of their last follow-up visit, it is recommended that the Investigator schedule a follow-up visit to determine the outcome of the event.

Safety Considerations

At any point in the study, or after the study has concluded, a subject can return for examination if needed. An on-call ophthalmologist will be available at all times, and subjects will be given emergency contact information.

Data Analysis

Data will be summarized by mean (SD) and compared for continuous variables, e.g. age, eyebrow excursion, etc., and frequency (%) for discrete variables, e.g. sex, end of effect at each follow up, etc. Eyebrow excursion and patient satisfaction at each follow up as well as duration of effect and pain score will be compared between the topical anesthetic pretreated and non-pretreatment groups using paired t-test; while percent of end of effect at each follow-up visit, rate of complications and subjective pain will be compared using McNemar test.

Data Storage and security

To insure the privacy of our participants, only contributors to the study will be allowed to review and discuss study data. Each participant will be assigned a study number upon enrollment into the study. All subject identifiers will be removed. Study data will be systematized in a spreadsheet with subject identification numbers, age, sex, order in which the measurements were taken.

Data collected will remain at the site of the study in a secured research office at Cizik Eye Clinic and will not be removed under any circumstance. All electronic data,

including photos, will be stored on password protected and encrypted devices and paper copies will be stored separate in a secured cabinet.

Ethics

IRB approval will be sought from the Committee for the Protection of Human Subjects (CPHS) for approval to recruit and enroll patients from the Robert Cizik Eye Clinic into this study.

All information collected about study subjects during this study will be kept confidential. Protected health information will be used only to identify patients enrolled in the study and will not be disclosed to anyone not directly involved in the study. Study documents will be stored in a secure location. A master list of participants will be generated on paper and electronic format. This list will be stored in a separate location from the data collection forms in a secured locked cabinet and encrypted desktop password protected computer. At the completion of data analysis, all data with protected health information will be destroyed/shredded.

All participants will be informed both verbally, and in the written informed consent, that there are no benefits or monetary compensation for participating in this research study. Participants will be given the opportunity to elect to have the botulinum injection without participation in the study, and participants will have the right to withdraw from the study at any time.

Written, informed consent will be obtained from all participants by a member of the investigative team.

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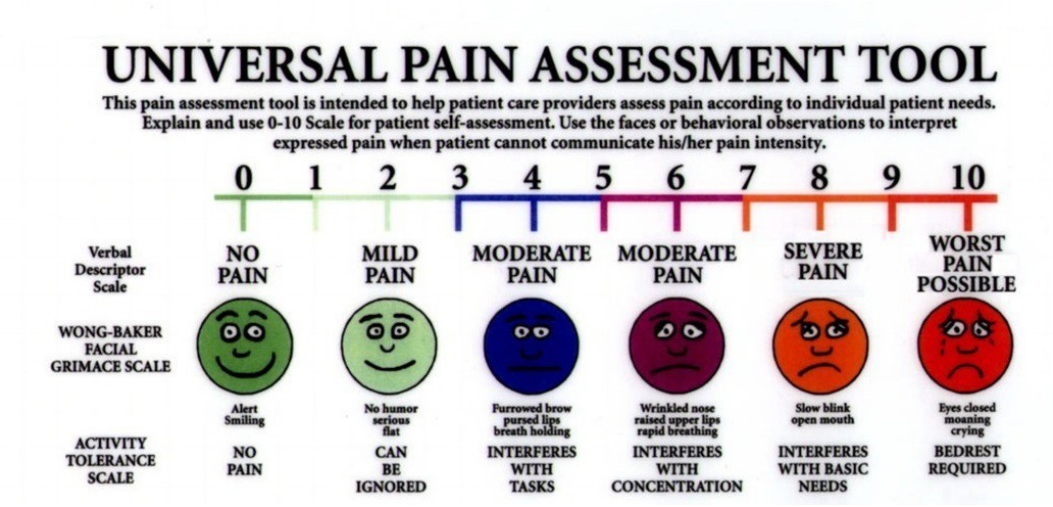
APPENDIX 1.


UNIVERSAL PAIN ASSESSMENT TOOL
This pain assessment tool is intended to help patient care providers assess pain according to individual patient needs. Explain and use 0-10 Scale for patient self-assessment. Use the faces or behavioral observations to interpret expressed pain when patient cannot communicate his/her pain intensity.
0 1 2 3 4 5 6 7 8 9 10
Verbal Descriptor Scale
NO PAIN
MILD PAIN
MODERATE PAIN
MODERATE PAIN
SEVERE PAIN
WORST PAIN POSSIBLE
WONG-BAKER FACIAL GRIMACE SCALE
Alert Smiling
No humor serious flat
Furrowed brow pursed lips breath holding
Wrinkled nose raised upper lips rapid breathing
Slow blink open mouth
Eyes closed moaning crying
ACTIVITY TOLERANCE SCALE
NO PAIN
CAN BE IGNORED
INTERFERES WITH TASKS
INTERFERES WITH CONCENTRATION
INTERFERES WITH BASIC NEEDS
BEDREST REQUIRED