Title: Botulinum toxin is a promising prophylactic therapy for minimizing post-excisional scarring: A Double Blinded, Randomized Controlled Trial

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A Double Blinded, Randomized Controlled Trial

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Introduction and Rationale:

Dermatological surgeons wear many hats to care for subjects with skin cancer. While their role in cancerous tissue removal results in superior cure rates, there is also a need for skilled excisional repair and effective wound healing regimens so the subject can heal with the least amount of scarring necessary. As such, numerous techniques have been developed for reducing the morbidity associated with excessive scarring. Various flaps and grafts allow the surgeon to approximate skin texture, thickness and adnexa with respect to the residual surrounding tissue. However, for optimal cosmetic and functional outcome, specific suture techniques are often necessary to ensure close wound approximation while simultaneously minimizing static tension along the wound edge (1). In addition, there are post-operative techniques for wound care that range from special dressings during the various stages of healing to cosmetic procedures for scar modification. Unfortunately, once the operation is complete, there is little the surgeon can do to minimize adverse scar formation without impairing the healing process. To date, most surgical wounds are allowed to heal at least partially before scar revision or modulation is attempted.

Botulinum toxin presents a unique opportunity for surgeons to affect scar formation throughout the duration of the healing process. These effects are likely independent and adjunctive to any and all wound care techniques, and are primarily attributed to a reduction in dynamic tension on the wound edges (1). Most importantly, botulinum toxin's one time dosing requirements with respect to reduced scar formation precludes the variance inherent to standard wound care practices.

Therefore, it has been proposed that for selected subjects, botulinum toxin may be a safe, effective and reliable means for improved post-excisional repair outcomes (2). Botulinum toxin has been investigated as an inhibitor of excessive, post-excisional scar formation in plastic surgery and Otorhinolaryngology literature (1-7). However, these promising studies have yet to combine objective assessment measures of human scar formation in a randomized controlled trial. In addition, there are currently no formal studies of botulinum toxin as a prophylactic against excess scarring in the dermatological literature. Fortunately, Botulinum toxin dosing in the forehead for the purposes of inhibiting excessive scar formation is comparable to the amount given for cosmetic purposes (5), which is commonplace in dermatology and well-studied (6-8).

Objective:

This study will attempt to assess the efficacy of Botulinum toxin as a prophylactic treatment in post-excisional repairs for the purpose of preventing excess scar formation. The end points will be the evaluation of each scar using the Manchester Scar Scale.

Description of Study:

We plan to enroll 40 subjects in this study who are scheduled for forehead excisions on the day of enrollment. Each qualifying subject will undergo post-excisional injections into the forehead and glabella. Twenty will receive 1ml of normal saline and 20 will receive a total of 50 units of botulinum toxin diluted in 1ml of normal saline. Both the subject and investigator will be blinded as to which site receives what. After these injections, the subject will proceed as per the normal standard of care for their post-operative care. Upon return for suture removal about a week later (as per normal standard of care), the subjects will all answer a brief questionnaire regarding any adverse events they may have had after the injections. They will then be scheduled for their last and only additional clinical visit for this study, at 24 weeks. Upon arrival for the final visit, the patient will again answer a brief questionnaire regarding any adverse events they may have had after the injections. After this, the assessment of response will be made utilizing the Manchester Scar Scale (MSS) both clinically and in a modified version via standardized photographs taken of the scar. The patient will then be discharged home, with their involvement in the study complete.

Method of injection:
Either 1ml of normal saline or 50 units of botulinum toxin diluted in 1ml of normal saline will be administered to a randomly assigned subject. The procedure will be identical for either substance. The forehead will be injected with 12, evenly spaced and symmetrical aliquots of 0.05ml and the glabella will be injected at the nasal root and the medial aspect of the corrugators with 0.1ml each in addition to the lateral aspect of each corrugator with 0.05ml. The injections will be administered with a 30G needle perpendicular to the skin. The following diagram (labeled figure 1) depicts the injection pattern:

Figure 1

*Large red circles represent areas for injecting 5units of Botox or 0.1ml of normal saline
*Small blue circles represent areas for injecting 2.5units of Botox or 0.05ml of normal saline

Response Measures:
The Manchester Scar Scale, a validated scale able to be used for linear surgical scars, will be applied in 2 ways (9-11). These 2 scores will then be added to yield the overall scar assessment score for each scar at each visit. Individual scores will be determined as follows:

1) Manchester Scar Scale (**MSS**)
The MSS will be used to clinically assess the scar of each subject at each visit with the following criteria clinical assessment sheet:

Clinical Assessment Sheet

Excellent		Visual Analogue Scale	Poor
	A	Color (cf. to surrounding skin)	
Lighter	☐	Perfect	1
or		Slight mismatch	2
Darker	☐	Obvious mismatch	3
		Gross mismatch	4
	B	Matte (1)/shiny (2)	
	C	Contour	
		Flush with surrounding skin	1
		Slightly proud/indented	2
		Hypertrophic	3
		Keloid	4
	D	Distortion	
		None	1
		Mild	2
		Moderate	3
		Severe	4
	E	Texture	
		Normal	1
		Just palpable	2
		Firm	3
		Hard	4

The Visual Analog Scale is on a 10cm line with a zero signifying the worst possible outcome and 100 representing the complete absence of noticeable scarring. This is a global, subjective assessment that is combined with a more objective assessment based on scar color, reflectance of light, contour, distortion and texture. A summation of the VAS score (rounded to the nearest cm) and the values assigned for each of the aforementioned assessment criteria will then be determined.

2) Modified Manchester Scar Scale (**mMSS**)
The mMSS will employ much of the MSS but will not include the assessment for texture since it will be applied to standardized photographs of each scar from each visit. Photographs will be taken at a distance of 10cm and cropped to include the scar and surrounding 1cm of normal skin. These photographs will then be assessed by a panel of Dermatologists at a later date. The scores will then be averaged to yield the mMSS average score for each scar at each visit.

Subject Selection:

Inclusion Criteria

1. English-speaking adults at least 18 years old.
2. Subjects must be scheduled for an excision of forehead skin due to any etiology, with a simple linear closure planned as the most likely surgical repair.
3. Subjects must be able to read, sign, and understand the informed consent.
4. Subject is willing and able to participate in the study as an outpatient, making several visits to the study center during the treatment and follow-up periods and to comply with all study requirements including concomitant medication and other treatment restrictions.
5. If subject is a female of childbearing potential she must have a negative urine pregnancy test result prior to study treatment initiation and must agree to use an approved method of birth control while enrolled in the study.

Exclusion Criteria

1. Subjects with an unstable medical condition as deemed by the clinical investigator, including review of the subject's prior and current medications.
2. Subjects with Myasthenia gravis, Lambert-Eaton Syndrome or other neuromuscular disorder.
3. Subjects taking medications that may alter the function of neuromuscular junctions (i.e. aminoglycoside antibiotics)
4. Women who are pregnant, lactating, or planning to become pregnant during the study period.
5. Subjects who have a history of keloids.
6. Known allergy to botulinum toxin.
7. Subjects who are not able to be closed with a simple linear technique

Informed Consent:

Prior to entering the study, the investigator or designated assistant will explain to each subject the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation. Subjects will be given the consent document, the opportunity to ask questions, and will be informed of their right to withdraw from the study at any time without prejudice. After this explanation and before any study-specific procedures have been performed, the subject will voluntarily sign and date and informed consent form, including photographic consent. Prior to participation in the study, the subject will receive a copy of the signed and dated written informed consent form.

Study Methodologies:

Visit 1 Screening/Baseline – Day 0 / Receive Injection

The following pre-study screening procedures should be completed prior to randomization and Treatment Initiation:

1. Obtain a signed and dated subject informed consent, including photographic authorization.
2. Review inclusion and exclusion criteria.
3. Collect demographic information including date of birth, sex, race, ethnicity, and underlying reason for excision.
4. If applicable, perform urine pregnancy testing.
5. After the excision is completed, the length of the defect will be recorded in addition to the number and type of sutures placed, final length of suture line and a photograph will be taken.
6. The subject will be randomly assigned to receive normal saline with or without botulinum toxin, prepared by outside party (recorded separately) and handed to dispensing physician and neither injector nor subject will know which.
7. Contents of syringe will be administered to forehead and glabella.
8. Schedule week 2 visit.

Visit 2 (Week 1 +/- 2 days, at suture removal as per normal standard of care)

The following procedures will be performed at this visit:

1. Review and record adverse events.
2. Sutures will be removed and unidentifiable photographs will be taken of the forehead.
3. Schedule final visit.

Visit 3 (Week 24 +/- 2 days)

The following procedures will be performed at this visit:

1. Review and record adverse events.
2. Subject will have their scar assessed clinically via the MSS and be photographed for later mMSS assessments.

Note: any treatment-related AEs or LSRs that are ongoing will be followed to resolution or to the investigator's satisfaction.

Primary Endpoints

1) Difference between treated and control MSS scores for each scar at 6 months
2) Difference between treated and control average mMSS scores for each scar at 6 months
3) Difference between treated and control aggregate scores for each scar at 6 months

Lesion Assessment Guidelines:

All MSS and mMSS assessments will be performed in a standardized fashion. The mMSS assessments will be blinded and performed by board-certified dermatologists in the Department of Dermatology, Faculty Practice Associates, Icahn School of Medicine at Mount Sinai, New York City.

Botulinum and Saline Injection Guidelines:

50 units of Botulinum toxin will be injected into randomly assigned subjects. The same procedure will be carried out for administration of the saline.

Safety Evaluations:

Urine Pregnancy Tests

Females of childbearing potential will undergo a urine pregnancy test at Visit 1(Week 0). If the pregnancy test is positive at Visit 1 the subject will not be permitted to enroll in the study and will not receive study drug.

Adverse Reactions

At each visit, the subjects will be assessed for any of the following possible AEs:
-injection site pain
-ecchymosis
-eyelid/brow ptosis
-systemic effects, including nausea, fatigue, malaise, flu-like symptoms, headache, runny nose, diplopia, dysarthria, generalized muscle weakness, asthenia, blurry vision, ptosis, dysphagia, dystonia, urinary incontinence, breathing difficulties, rash.

Prior and Concomitant Medications:

At the initial visit, prior and concomitant medications and therapies will be reviewed as may pertain to exclusion from the study.

Restricted Medications/Treatments

Restricted medications and treatments prior to the study initiation are those that the investigator feels may indicate that the subject has an unstable medical condition, as described in the exclusionary criteria.

Subject Withdrawal or Discontinuation:

Subjects may choose to withdraw from the study or may be withdrawn by the investigator at any time without prejudice to their future medical care. Any subject who does not comply with the inclusion/exclusion criteria may be withdrawn from further participation in the study.

Discontinuation Procedures: Any subject who wishes to discontinue prematurely from the study should return to the study center for an End of Study Visit.

Adverse Event Definitions:

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject which is temporally related to protocol procedures, including administration of a pharmaceutical product at any dose, but which does not necessarily have a causal relationship with the treatment. The term AE also applies to laboratory findings or results of other diagnostic procedures that are considered to be clinically relevant (e.g., that required unscheduled diagnostic procedures or treatment measures or result in withdrawal from the study). Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an adverse event, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not adverse events, if the condition(s) was (were) known before the start of study treatment.

Adverse events will be recorded according to CTCAE guidelines.

A serious adverse event (SAE) is any AE or adverse drug reaction that at any dose results in any of the following outcomes:

- death
- life-threatening adverse event
- inpatient hospitalization or prolongation of existing hospitalization
- persistent or significant disability/incapacity
- congenital anomaly/birth defect

An event may be considered serious when, based upon appropriate medical judgment, it jeopardizes the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

A life-threatening adverse event is any AE or adverse drug reaction that at any dose places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not include a reaction or event that, had it occurred in a more severe form, might have caused death.

Materials and Supplies:

Study Drug
Botox botulinum toxin will be used for this study, a grant from Allergan to provide drug is pending. Normal saline will be used as the placebo.
1cc Syringes and 30 G needles will be used.
Gauze and alcohol swabs will be used to prepare the injection sites.

Institutional Review Board:

Prior to beginning this study, approval must be obtained from the Institutional Review Board at the Icahn School of Medicine at Mount Sinai.

Data Analysis:

Individual Manchester Scar Scale and modified Manchester Scar Scale scores will be summed and plotted in each group and the medians of each group will be assessed using the Wilcoxon Rank Sum Test to determine if the results are statistically significant.

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