Botulinum Toxin to improve cosmesis of primary cleft lip repair

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Protocol Title:	Botulinum Toxin to improve cosmesis of primary cleft lip repair
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Co-Mentor/Preceptor:	Dr. Amber Luong, MD
Population:	Pediatric patients requiring a primary cleft lip repair younger than 6 months of age. Goal of 40 patients total enrolled.
Number of Sites:	UT Health – Memorial Hermann Hospital – Texas Medical Center
Study Duration:	7/1/2014 – 6/30/2016
Subject Duration:	From pre-operative assessment to minimum 1 year follow up

General Information

- Primary cleft lip repairs are most frequently done at 3 months of age. There are many factors that influence the final cosmetic appearance of the repair including wound tension. Unacceptable amounts of tension can lead to poor cosmetic appearance, wound dehiscence or fistula formation. Use of Botulinum toxin intraoperatively can reduce wound tension and therefore improve outcomes of cleft lip repairs.

Background Information

- Hypothesis: Utilizing Botulinum toxin intraoperatively during primary cleft lip repair will improve the cosmetic appearance of cleft lip scars. Patients with unilateral cleft lips with or without cleft palates will beconsidered.
- Few studies have been done utilizing botulinum toxin to improve outcomes of cleft lip repairs. Cleft lip repair outcomes are influenced by a number of factors including wound tension. Wound tension is often unavoidable in these patients due to continuous muscle contraction from crying or feeding. Therefore, limiting muscle contraction could potentially improve outcomes of these repairs. Tollefson et al. in 2006 reported the first study with targeted injections of botulinum toxin into the orbicularis oris in the cleft lip of patients younger than 6 months old. All three patients showed exceptional post-operative aesthetic outcomes at early follow up without any complications.
- The need to chemoimmobilze musculature associated with cleft lip repair is of even greater importance as multiple studies have shown increased activity of these muscles. Carvajal et al. established that orbicularis oris activity was significantly greater in cleft lip and palate patients than those children without clefts. Aside from the impact this can have on the growing maxilla this increased muscle activity can be problematic for cleft lip repair cosmesis.
- In 2009, Galárraga used intraoperative botulinum toxin on 5 patients all younger than 6 months of age undergoing a primary cheiloplasty. The study showed the botulinum toxin injections to be safe without any complications observed. An EMG proven decrease in muscle activity around the repair site was also seen as predicted.
- Studies in adult patients have shown improved cosmetic outcomes for facial wounds when utilizing botulinum toxin. They have also established use of the toxin as safe in the face. Ziade et al. in 2013 showed injections of botulinum toxin type A within 72 hours postoperatively around facial wound repairs had better scar results at 1 year follow up as analyzed by 6 expert specialists. Wilson in 2006, showed utilization of botulinum toxin in revision facial scar surgery had 90 % of patients with a highly satisfactory outcome.

Objectives

Improve cheiloplasty outcomes with the use of intraoperative injection of botulinum toxin to clefted lip.

Study Design

- Randomized double blinded controlled trial of pediatric patients who require a primary unilateral cleft lip repair younger than 6 months of age. Utilization of botulinum toxin intraoperatively at targeted locations of the cleft lip. Surgeon, parents and expert panel of surgeons used at the completion study will all be blinded to which patients received the experimental injection.
- Control subjects will receive injections of normal saline at identical sites of the cleft lip as experimental subjects.
- 20 patients in each group will be enrolled.
- Patients will be evaluated preoperatively, postoperatively at 1 week, 1 month, 3 months, 6 months and 12 months of follow up.
- **Inclusion criteria**: Unilateral cleft lip with or without cleft palate, less than 6 months of age
- **Exclusion criteria**: Bilateral cleft lip, older than 6 months of age
- Primary endpoint: Blinded assessment of wound cosmesis by plastic surgeons and parents using scar assessment scale. At completion of follow up use of aesthetic grading criteria of videography images as described by Reddy et al. in 2008. These criteria include: Matching accuracy of white roll and vermilion border, scar appearance, Cupid's bow form, length of lip, nostril symmetry, alar dome form, and alar base position

Study Population

- Pediatric patients with complete unilateral cleft lip and palate less than 6 months of age undergoing cleft lip repair.
- All patients who will be planned for a primary cleft lip repair will be offered to be enrolled in the study. Parents may choose to decline and undergo repair without enrollment in the study.
- Patients will be recruited as they would present otherwise to the University of Texas Pediatric Plastic Surgery Clinic to be evaluated for repair of cleft lip.

Study Procedures

- Patient will receive intraoperative botulinum toxin injections in the upper labial musculature prior to the operative repair being started.
- 4 injection sites will be used two superior and inferiorly in the cleft lip, 1 unit of botulinum toxin per injection site to be used. This is considered low dose in the pediatric population. Depending on the patient's weight it will be approximately 1 unit/kg.
- This dosing was chosen as it has been proven safe without any complications in prior pediatric botulinum toxin studies.
- This dosage has also been shown to adequately elicit muscle paresis in the head and neck.
- Patients will have videography performed preoperatively as well at scheduled post-operative visits.
- Parents will complete a Modified Vancouver Scar Scale at selective post-operative visits
- The Vancouver scar scale is a widely used validated scar scale for adults, however given our study it was modified appropriately for pediatric populations. There is no validated scar scale for pediatric patients.
- At the completion of the 1 year follow up period, videography will be sent to an expert panel of select plastic surgeons that will also use the Modified Vancouver Scar Scale to assess scar outcomes in both the control and experimental groups. This panel will be blinded to which patients received botulinum toxin and which received the control injection.
- Videography at the completion of the study will also be assessed for the following measures: Matching accuracy of white roll and vermilion border, scar appearance, Cupid's bow form, length of lip, nostril symmetry, alar dome form, and alar base position. Study personnel will be blinded to which patients received the experimental injection.
- No invasive procedures or postoperative monitoring will be employed unless deemed medically necessary.

Block Randomization

Block randomization will be used for this study. The size of the blocks will not be fixed to ensure surgeons are truly blinded along with each arm of the study having the same number of patients. Therefore each group may have block sizes of 3, 5, 2, 6 and 4 to allow for a total of 20 patients. Both the ordering of blocks and their respective size will be blinded to eliminate any selection bias.

Drug Administration and Accountability

Dr. Jaecel Shah MD, Dr. Matthew Greives, MD and John Teichgraeber, MD will be responsible for botulinum toxin accountability. The toxin will be stored with the operating room pharmacy. As the study will be a randomized controlled trial, for those patients set to receive botulinum toxin, the medication will be requested from the OR pharmacy on the day of surgery. Prior to surgery it will be ensured the OR pharmacy has the toxin available. The toxin will be mixed as prescribed and 1 unit injections at 4 distinct sites will be used for a total of 4 units administered.

The pediatric plastic surgery research nurse will be responsible for notifying the operating room circulator whether that days block of patients will be receiving the experimental versus the control injection.

Study patients will be attempted to be scheduled on the same OR days to maximize utilization of each botulinum toxin vial as they have a limited shelf life once mixed. Once the vial has been utilized it will be dispensed appropriately. The vials in the OR pharmacy will be stored in a standard cooled refrigerator as recommend by the manufacturer.

Possible Risks to Subjects

- Botulinum toxin safety has been well established. The FDA endorses that botulinum toxin use in a dermatologic fashion have no reported adverse side effects at the recommended doses. Studies which have utilized botulinum toxin in patients younger than 6 months of age have not reported significant adverse effects.
- Transient fatigue lasting no longer than 96 hours has been noted in a study by Pascual and Pascual in 2008 in one patient out of 74.
- The likelihood of risks are low and most studies have showed no side effects while few studies have noted transient fatigue in less than 5% of patients.
- Given that botulinum toxin takes 72 hours minimum to take effect there will be no change in the surgical procedure. Therefore there is no significant change in risk of the surgery itself.
- Also of note this study will be using botulinum toxin doses lower than most studies already completed, therefore the risk should be less as the risk of botulinum toxin is dose dependent.
- Two prior cleft lip studies utilizing botulinum toxin reported good outcomes with no complications or feeding difficulties.

Rare reported adult adverse side effects of botulinum toxin include: Difficulty swallowing, breathing, speaking, feeding, diffuse muscle weakness, double vision, voice changes, allergic reaction and bladder dysfunction. However, no documented adverse effects have been noted when used at dermatologic doses on the face.

Safety

- Two studies on cleft lip patients younger than 6 months of age utilizing botulinum toxin have been completed without any complications and shown the toxin to be safe in this population.

Prior cleft specific studies

- Tollefson et al. in 2006 with 3 patients and Galarraga in 2009 with 5 patients used botulinum toxin injections in the cleft lip without any reported complications.

Prior pediatric botulinum toxin studies

- Botulinum toxin injections are also used for a large variety of pediatric conditions safely including ophthalmologic, gastrointestinal and neurological.

- Messner et al. in 2011 used 7 botulinum toxin injections in 3 patients younger than 6 months of age with for cricopharyngeal achalasia. Injections were done in the cricopharyngeus muscle with successful treatment allowing patients to eat by mouth as a result. No complications were encountered with an average follow up of 22 months, 3.3units/kg of botulinum toxin were used.

- Pascual and Pascual in 2008, reviewed botulinum toxin injection safety in patients younger than 2 years old. 74 patients received botulinum toxin injections with 28 younger than 1 year of age. Only 1 patient was noted to develop transient fatigue that lasted less than 4 days without intervention. All other patients did well with no significant adverse effects. On average 6.55 units/kg for patients less than 1 year of age and 8.4 units/kg in patients 1-2 years old were used. They deemed botulinum toxin injections safe at the appropriate dosage.

- Chhina et al. in 2013 showed higher dosages of botulinum toxin were safe in patients less than 2 years of age. Injections were done in the feet on patients with clubfeet. 239 patients and 361 feet were injected with 10 units/kg. No complications were noted in any patient and again deemed botulinum toxin injections safe.

- Oleszek et al. in 2005 performed botulinum toxin injections for patients aged 6-18 months with congenital torticollis. 29.7 units of botulinum toxin were used on average for each patient. Only 2 patients had transient neck weakness with mild dysphagia that resolved without intervention. They showed that even at higher doses botulinum toxin was safe to use in the head and neck.

- Of note our study will only use a low dose of 4 units of botulinum toxin total and will approximately be 1 unit/kg dosing depending on the weight of our study patient. This dosage is less than most pediatric botulinum toxin injection studies to date and therefore should be a safe dosage.

- As noted above a large number of studies have shown botulinum toxin to be safe at both low and high doses at a variety of anatomic locations including the head and neck.

Safety Monitoring

The PI, co-investigator and mentor will review any reported adverse events monthly.

- Patients feeding capabilities, respiratory status, neuromuscular function and overall health will be evaluated on each scheduled follow up visit.

Statistics

- Using the Modified Vancouver Scar Scale we hypothesize the average score for controls to be 7 out of 11. For experimental patients we expect an average score of 10 out of 11. Given a 90% confidence interval and standard deviation of 2.5 the necessary sample size would be 15 subjects per group using a 2 sided test.
- Therefore 20 patients will be the goal group size for each arm of the study; botulinum toxin injection group versus control group.
- The study will be terminated if any subjects display significant adverse side effects that are potentially life threatening including feeding, cardiovascular or respiratory complications.
- Study subjects to be used will be all patients who will undergo a primary cleft lip repair that agree to participation in the study and subsequent randomization.

Ethics

- Prior to initiating the study University of Texas Health Science Center at Houston Institutional Review Board will need to grant approval for the study.
- Consent will be obtained in person at the time of the pre-operative visit in the University of Texas Pediatric Plastic Surgery clinic. This consent will be in addition to the consent obtained for the surgical procedure. The known risks and adverse effects of botulinum toxin will be fully disclosed to parents prior to obtaining consent for the study.

- Consent will also be required to be obtained for videography that will be used pre/post operatively to evaluate cosmesis of the repair.

Data handling and record keeping

- Operative reports will be securely located in the Care4 EMR of Memorial Hermann Hospital which is the hospital affiliated with the University of Texas Medical School at Houston where the cleft lip repairs will occur.
- All data will be securely located on a LOK IT secure flash drive as approved by the University of Texas Medical School at Houston. LOK IT secure flash drive is password coded and identified as a suitable way to store patient sensitive data.
- Videography will also be kept on this secure LOK IT flash drive to ensure confidentiality.
- A computer supplied and maintained by the University of Texas Medical School at Houston that is in the Otolaryngology resident work room will be the main computer used when accessing and analyzing data/images. The computer is password protected and is approved for use by the medical school for data collection use.
- Images of the patient will only include the face to assess the outcomes of the repair. All images taken at planned post-operative visits will be taken with the same camera and calibration settings.
- Data and images will be coded by a discrete number that will be used to identify an individual patient and their repair. No patient identifiers will be linked to the videos

Quality control and assurance

- Videography camera will be operated by a select number of users that have been taught the appropriate amount of training to operate it appropriately.
- Camera will be calibrated prior to each session to ensure consistent videography.
- A modified Vancouver Scar Scale will be given to parents at post-operative visits.
- Botulinum toxin will be prepared in the same manner for each patient.

Publication Plan

- Plan to submit abstract and manuscript to reputable conferences and otolaryngology journals at the completion of the study.

ATTACHMENTS

1. Study Schedule
2. Consent Document
3. Modified Vancouver Scar Scale
4. Aesthetic grading criteria table

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