Document Cover Page

Study Title: Comparison Study of LMX4 Cream Versus J-Tip Needle Free Injection System with Lidocaine for In-Office PAT for Clubfoot

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A Randomized, Comparison Study of L.M.X.4 Cream versus J-Tip Needle-Free Injection System with Lidocaine in Children Undergoing In- Office Percutaneous Achilles Tenotomy for Clubfoot

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1.0 Background

Congenital idiopathic clubfoot is defined as “a complex foot deformity that occurs in an otherwise normal child” (Morcuende, Dolan, Dietz, & Ponseti, 2004). Despite idiopathic clubfoot being due to unknown causes and occurring in approximately every 1 in 1000 live births, it is often easily treated (Ansar et.al, 2018). Ignacio V. Ponseti was the leading pioneer in researching and treating clubfeet in infants and his methods are widely used today. “The Ponseti method is a safe and effective treatment for congenital idiopathic clubfoot and radically decreases the need for extensive corrective surgery” (Morcuende, Dolan, Dietz, & Ponseti, 2004). “This method involves weekly stretching of the deformity followed by application of a long-leg cast. All components of the deformity usually correct within 4 to 5 weeks with the exception of the equinus. A simple percutaneous tendoachilles tenotomy often is necessary to correct completely the equinus” (Morcuende, Dolan, Dietz, & Ponseti, 2004). “After the tenotomy, a final cast is applied and left in place for 3 weeks to allow for healing to occur in the correct position. When the last cast is removed, the patient is treated with abduction splinting with straight-last shoes and a Denis Browne-style bar set at 45 degrees external rotation for the normal foot and 70 degrees for the clubfoot. In bilateral cases both feet are set at 70 degrees of external rotation. The protocol for this foot abduction orthosis is 23 hours per day for the first 3 months and then nighttime only for 2 to 4 years. This process is essential to avoid recurrence” (Herzenberg, Radler, & Bor, 2002) “The goal of treatment is to correct all components of the deformity so that the patient has a pain-free, plantigrade foot with good mobility, without calluses, and without the need to wear special or modified shoes in the future” (Morcuende, Dolan, Dietz, & Ponseti, 2004). Several studies have supported Ponseti’s methods of casting and discovered positive results, primarily avoiding Posteromedial Release (PMR), an extensive open surgery (Herzenberg, Radler, Bor, 2002). This treatment also resulted in a decreased number of patients whose clubfoot relapsed following treatment by the Ponseti method (Morcuende, Dolan, Dietz, & Ponseti, 2004).

One defining characteristic to Ponseti’s method is the addition of the percutaneous Achilles Tenotomy a small procedure which has been shown to avoid PMR in 95% of cases. Because PMR was found to lead to long term stiffness and weakness and involved greater surgical intervention, the percutaneous Achilles tenotomy was implemented (Herzenberg, Radler, Bor, 2002). The percutaneous Achilles Tenotomy entails releasing the tendon with a scalpel blade and dorsiflexing the foot in order to correct the equinus, followed by the application of a long leg cast (Lebel et. Al, 2012) (Morcuende, Dolan, Dietz, & Ponseti, 2004). Percutaneous Achilles Tenotomies have been successfully performed in the operating room under general anesthesia and in an outpatient clinic setting utilizing local or topical anesthesia. Ponseti and others have performed the procedure as an in-office procedure under sterile conditions, yielding a rate of successful “nonsurgical” correction of clubfoot approaching 90% of cases.” Performing this procedure in office has proven to be safe, yielding a low number of post-operative emergency room visits due to complications or parental concerns (Lebel et. Al, 2012).

While studies have shown that in office percutaneous achilles tenotomies are safe and efficient, little has been done to investigate the pain management strategies implemented for infants during this procedure. As healthcare professionals working with infants, "the prevention of pain in neonates should held as highly as the treatment being provided not only because it is ethical, but also because research has proven that repeated painful exposures during early stages of life have the potential for deleterious consequences" (American Academy of Pediatrics, 2016). Those consequences include, but aren't limited to, "alterations in hemodynamic stability, altered stress hormone expression, heightened peripheral sensitivity, altered pain reactivity that persists following the painful stimulus, and somatization" (Stevens et. Al, 2014) One study identified the infant's ability to become conditioned to painful stimuli, such as heel lances, at as early as 3 days old (Taddio, Shah, Gilbert-MacLeod, & Katz, 2002). With this information in mind, healthcare providers should be prepared to provide adequate pain management for infants during painful procedures by utilizing non-pharmaceutical techniques, pharmaceutical techniques, or a combination of both.

During in office percutaneous Achilles tenotomies, several studies mention the use of topical anesthesia, such as EMLA, a Lidocaine/Prilocaine cream. This cream is applied to the infant's skin surrounding the heel cord and requires 30 minutes to provide numbness reaching a depth of up to 5 mm at maximum effect (Fox, Tobin, & Aria, 2016). Pershad, Steinberg, & Waters, 2008, study reported that a 5-gram tube of ELMA cream cost the hospital $7.69, regardless of volume used from the tube. Other institutions have reported 25 grams of EMLA cream reaching $56.00. Due to clinical observation and medical advancements, there is room to believe that time efficient and cost-effective methods of providing greater pharmaceutical pain management to clubfoot infants during this procedure are available.

The J-tip is a needle-free jet injection system that uses compressed CO2 instead of a needle to push .25 ml of lidocaine into the skin, providing a local anesthetic at the site of administration in less than a minute" (Lunoe, et al., 2015). The J-tip provides numbness to the site of application at a depth of 5- 8 mm (Fox, Tobin, & Aria, 2016). Pershad, Steinberg, & Waters, 2008, reported, in the same study referencing EMLA cream prices, that the Needle-free jet injection device price per cartridge and .25 mL of buffered Lidocaine cost the hospital $2.10. Through various studies, the J-Tip has been proven to provide greater pain management than other pharmaceutical options, including EMLA cream and vapocoolant spray (Spanos, et al. 2008).

2.0 Hypothesis and Specific Aims

Aim 1: Determine which pain management method, L.M.X.4 Cream vs. J-tip 1% Xylocaine MPF Injection, provides the greatest pain relief to infants with clubfoot undergoing an in-office percutaneous TAL.

Hypothesis: J-tip 1% Xylocaine MPF injection will provide equal or greater pain control when compared to L.M.X.4 cream in infants undergoing an in-office percutaneous TAL.

Aim 2: Determine if there is a difference in the rate of adverse events between the two pain management methods, L.M.X.4 Cream vs. J-tip 1% Xylocaine MPF Injection.
Hypothesis: J-tip 1% Xylocaine MPF injection will not be associated with an increased rate of adverse events in comparison to L.M.X.4 cream in infants undergoing an in-office percutaneous TAL.

3.0 Animal Studies and Previous Human Studies

The below studies reference 4% ELA-Max cream and EMLA cream. ELA-Max is the former name of L.M.X.4 cream. EMLA cream is similar to the L.M.X.4 cream used by Vanderbilt Pediatric Orthopaedic physicians during routine care tenotomies for pain relief. L.M.X.4 cream is an over the counter medication with an active ingredient of Lidocaine 4%. EMLA cream is a prescription only medication with active ingredients of Lidocaine 2.5%/Prilocaine 2.5%.

Pediatr Emerg Care. 2008 Aug;24(8):511-5. doi: 10.1097/PEC.0b013e31816a8d5b.
Jet Injection of 1% buffered lidocaine versus topical ELA-Max for anesthesia before peripheral intravenous catheterization in children: a randomized controlled trial.
Spanos S, Booth R, Koenig H, Sikes K, Gracely E, Kim IK.

Abstract
BACKGROUND:
Peripheral intravenous (PIV) catheter insertion is a frequent, painful procedure that is often performed with little or no anesthesia. Current approaches that minimize pain for PIV catheter insertion have several limitations: significant delay for onset of anesthesia, inadequate anesthesia, infectious disease exposure risk from needlestick injuries, and patients' needle phobia.
OBJECTIVE:
Comparison of the anesthetic effectiveness of J-Tip needle-free jet injection of 1% buffered lidocaine to the anesthetic effectiveness of topical 4% ELA-Max for PIV catheter insertion.
METHODS:
A prospective, block-randomized, controlled trial comparing J-Tip jet injection of 1% buffered lidocaine to a 30-minute application of 4% ELA-Max for
topical anesthesia in children 8 to 15 years old presenting to a tertiary care pediatric emergency department for PIV catheter insertion. All subjects recorded self-reported visual analog scale (VAS) scores for pain at time of enrollment and pain felt following PIV catheter insertion. Jet injection subjects also recorded pain of jet injection. Subjects were videotaped during jet injection and PIV catheter insertion. Videotapes were reviewed by a single blinded reviewer for observer-reported VAS pain scores for jet injection and PIV catheter insertion.

RESULTS:
Of the 70 children enrolled, 35 were randomized to the J-Tip jet injection group and 35 to the ELA-Max group. Patient-recorded enrollment VAS scores for pain were similar between groups (P = 0.74). Patient-recorded VAS scores were significantly different between groups immediately after PIV catheter insertion (17.3 for J-Tip jet injection vs 44.6 for ELA-Max, P < 0.001). Blinded reviewer assessed VAS scores for pain after PIV catheter insertion demonstrated a similar trend, but the comparison was not statistically significant (21.7 for J-Tip jet injection vs 31.9 ELA-Max, P = 0.23).
CONCLUSION:
J-Tip jet injection of 1% buffered lidocaine provided greater anesthesia than a 30-minute application of ELA-Max according to patient self-assessment of pain for children aged 8 to 15 years undergoing PIV catheter insertion.
TRIAL REGISTRATION: ClinicalTrials.gov NCT00444756.

Acad Emerg Med. 2018 Mar;25(3):310-316. doi: 10.1111/acem.13351. Epub 2017 Dec 26. A Randomized Double Blind Trial of Needle-free Injected Lidocaine Versus Topical Anesthesia for Infant Lumbar Puncture.
Caltagirone R Raghavan VR, Adelgais K, Roosevelt GE.

OBJECTIVES:
Lumbar punctures (LPs) are commonly performed in febrile infants to evaluate for meningitis, and local anesthesia increases the likelihood of LP success. Traditional methods of local anesthesia require injection that may be painful or topical application that is not effective immediately. Recent advances in needle-free jet injection may offer a rapid alternative to these modalities. We compared a needle-free jet-injection system (J-Tip) with 1% buffered lidocaine to topical anesthetic (TA) cream for local anesthesia in infant LPs.
METHODS:
This was a single-center randomized double-blind trial of J-Tip versus TA for infant LPs in an urban tertiary care children's hospital emergency department. A computer randomization model was used to allocate patients to either intervention. Patients aged 0 to 4 months were randomized to J-Tip syringe containing 1% lidocaine and a placebo TA cream or J-Tip syringe containing saline and TA. The primary outcome was the difference between the Neonatal Faces Coding Scale (NFCS) before the procedure and during LP needle insertion. Secondary outcomes included changes in heart rate (HR) and NFCS throughout the procedure, difficulty with LP, number of LP attempts, provider impression of pain control, additional use of lidocaine, skin changes at LP site, and LP success.
RESULTS:
We enrolled 66 subjects; 32 were randomized to J-Tip with lidocaine and 34 to EMLA. Six participants were excluded from the final analysis due to age greater than 4 months, and the remaining 58 were analyzed in their respective groups (32 J-Tip, 34 TA). There was no difference detected in NFCS between the two treatment groups before the procedure and during needle insertion for the LP (p = 0.58, p = 0.37). Neither HR nor

NCFS differed among the groups throughout the procedure. Median perception of pain control by the provider and the need for additional lidocaine were comparable across groups. LPs performed with a J-Tip were twice as likely to be successful compared to those performed using TA (relative risk = 2.0; 95% confidence interval = 1.01-3.93; p = 0.04) with no difference in level of training or number of prior LPs performed by providers.
CONCLUSIONS:
In a randomized controlled trial of two modalities for local anesthesia in infant LPs, J-Tip was not superior to TA cream as measured by pain control or physiologic changes. Infant LPs performed with J-Tip were twice as likely to be successful.
TRIAL REGISTRATION:
ClinicalTrials.gov NCT01628874.

J Pediatr Nurs. 2017 Nov - Dec;37:91-96. doi: 10.1016/j.pedn.2017.08.025. Epub 2017 Aug 18. Comparison of Children's Venipuncture Fear and Pain: Randomized Controlled Trial of EMLA® and J-Tip Needleless Injection System®.
Stoltz P, Manworren RCB.

PURPOSE:
Needle procedures, like venipuncture and intravenous (IV) catheter insertion, are recognized as a common cause of pain and fear for children in hospitals and emergency departments. The purpose of this study was to compare children's self-reported pain and fear related to IV insertion with administration of either the topical local anesthetic EMLA® or 1% buffered lidocaine delivered with the J-Tip Needleless Injection System® (J-Tip®).
DESIGN AND METHODS:
In this prospective, randomized trial, 150 consecutive pediatric patients 8 to 18years of age undergoing IV insertion were randomly assigned 1:1 to treatment group. Participants self-reported procedural pain using a Visual Analog Scale, and procedural fear using the Children's Fear Scale.
RESULTS:
Procedural pain scores were significantly lower in the EMLA® group (mean score 1.63+1.659) vs. the J-Tip® group (2.99±2.586; p<0.001). Post-procedure fear scores were significantly lower than pre-procedure fear scores in both treatment groups (p<0.002), but there was no difference in fear scores between the two treatment groups (p=0.314).
CONCLUSION:
EMLA® provided superior pain relief for IV insertion compared to J-Tip®.
PRACTICE IMPLICATIONS:
Although EMLA® use resulted in lower self-reported pain scores compared to J-Tip®, pain scores for both treatments were low and fear scores did not differ. When IV insertion can be delayed for 60-90min, EMLA® should be used. When a delay is contraindicated, J-Tip® may be a reasonable alternative to minimize procedural pain of IV insertion.

Anesth Analg. 2006 Feb;102(2):411-4.
A comparison of a needle-free injection system for local anesthesia versus EMLA for intravenous catheter insertion in the pediatric patient.
Jimenez N, Bradford H, Seidel KD, Sousa M, Lynn AM.
Abstract
Placement of IV catheters is a painful and stressful procedure for children. J-Tip is a needle-less Food and Drug Administration approved injection system that can be used for delivery of local anesthetic before IV cannulation. In this study, we compared the effectiveness of J-Tip versus eutectic mixture of local anesthetics (EMLA) to facilitate IV cannulation and provide adequate analgesia before IV placement. Children 7-19 years of age (n = 116) were randomized to receive 0.25 mL of 1% buffered lidocaine with J-Tip (n = 57) or 2.5 g of EMLA (n = 59) before IV cannulation. Measurements of success of cannulation (number of attempts for IV placement) and pain (0-10 visual analog scale) at application of local anesthetic and at cannulation were performed. There was a significant (P = 0.0001) difference in pain ratings during IV cannulation between EMLA (median = 3) and the J-Tip (median = 0). Eighty-four percent of patients reported no pain at the time of J-Tip lidocaine application compared to 61% in the EMLA group at the time of dressing removal (P = 0.004). We did not find differences in the number of attempts for IV cannulation. J-Tip application of 1% buffered lidocaine before IV cannulation is not painful and has better anesthetic effectiveness compared with EMLA.

Study personnel is not aware of any previous studies comparing J-Tip with 1% Buffered Lidocaine to EMLA cream for pain management in infants with clubfoot undergoing a percutaneous Achilles tenotomy.

4.0 Inclusion/Exclusion Criteria

Inclusion Criteria

- Clubfoot patients less than 6 weeks of age at start of casting
- Patients presenting to Vanderbilt DOT 4 Clinic for care
- Patients undergoing in-clinic Achilles Tenotomy

Exclusion Criteria

- Clubfoot patients greater than 6 weeks of age at the start of casting
- Previous clubfoot treatment
- Patients with a neuromuscular condition (spina bifida, caudal regression syndrome, arthrogryposis, etc.)
- In-office TAL is not recommended by treating physician due to patient factors such as age or size

5.0 Enrollment/Randomization

Enrollment

General inclusion/exclusion criteria will be used to determine patient eligibility for this study. Potential study participants will be identified when they present to the Vanderbilt Children's Orthopaedic or Texas Scottish Rite Hospital for Children clinics for treatment of presumed congenital idiopathic clubfoot.

In-person Consent Process

When a patient is determined to be eligible for the study, study personnel will approach the patient's parent(s)/legal guardian(s) about taking part in the study. If the patient's parent(s)/legal guardian(s) agree for their child to participate in the study, they will be provided with an informed consent document to review. The consent process will be conducted using either 1) a paper version of the appropriate consent form or 2) a REDCap-based electronic consent form. The electronic consent form has been developed in REDCap, a secure, web-based, HIPAA-compliant, data collection platform with a user management system. The REDCap-based electronic consent form can be accessed by research personnel using any electronic device. They will be given an opportunity to ask questions about the study. If the patient's parent(s)/legal guardian(s) agree for their child to participate in the study by signing the informed consent document, they will be provided with a copy of the signed consent form for their records. Only one parent/legal guardian signature will be required for this study.

Electronic Consent Process:

In the event a potential study candidate is missed during a clinic visit, or research personnel are unavailable to consent in-person, study personnel will contact the patient's parent(s)/legal guardian(s) by phone to notify them of their child's study eligibility and ask if they would be interested in their child taking part. If the parent(s)/legal guardian(s) are interested in their child taking part in the study, study personnel will send a link to the REDCap-based electronic consent form by e-mail. If the parent(s)/legal guardian(s) agree for their child to take part in the study after reading the informed consent document, there will be an option for one parent/legal guardian to electronically sign their name and date the informed consent document. Once they electronically sign the electronic informed consent document, they will be given an option to save or print the signed electronic informed consent documents for their files.

We will seek to enroll 47 patients per group, 94 patients total in this study at each site.

Randomization

The patients will be randomized in equal proportion (1:1) to either the *control group* (receive L.M.X.4 cream with J-Tip saline injection) or the *intervention*

group (placebo cream with J-Tip with 0.25mL of 1% Xylocaine MPF). Randomization will take place on or after the final casting visit. A randomization allocation table created by statisticians will be uploaded into REDCap. The research coordinator will access the randomization module in REDCap and randomize the participant. Patients will not be randomized until they are definitively diagnosed with congenital idiopathic clubfoot that requires a tenotomy and consented for participation in the study.

6.0 Study Procedures

Weekly Casting Visits

Once study consent is obtained, the subject will undergo serial casting weekly by one of two board-certified Pediatric Orthopaedic surgeons using the Ponseti method to address their congenital idiopathic clubfoot. CCLS will be present to provide coping support and standardize the environment. This is routine care at our institution. During these castings, patient will wear pulse ox on hand, with mitten covering tool if needed, in order to measure heart rate and oxygen saturation. The CCLS, with assistance from a trained research assistant, will assess the subject's pain and temperament utilizing observational data and data collected from FLACC Scale. Observational assessment is also routine care, but the FLACC data, pulse ox and temperament questionnaire are new, being collected strictly for the study. Primary data will be obtained during casting of first foot and, in the case of bilateral clubfoot patients, a subgroup will be created utilizing data collected during casting of both feet.

Data collection during weekly castings will be obtained by a trained research assistant and will be event based, utilizing pulse ox and FLACC scale. Time points are as follows:

- Baseline before cast placement (patient placed on treatment table)
- Start of casting, after cast padding placed (1st cast if bilateral)
- End of casting (2nd cast if bilateral)

If the subject does not require tenotomy after the weekly casting, they will be withdrawn from the study.

Casting Visit 1 Week Prior to Tenotomy

During the final casting visit prior to the subject's tenotomy, the subject's temperament will be assessed by the parents and CCLS by utilizing:

- An adapted temperament questionnaire for parents (research only)
- Assessment of subject over time by CCLS utilizing FLACC scale, O2, HR and chart notes.

On the day of or after the final casting visit, the participant will be randomized in equal proportion (1:1) to either the *control group* (receive L.M.X.4 cream with J-Tip saline injection) or the *intervention group* (placebo cream with J-Tip with 0.25mL of 1% Xylocaine

MPF). Researchers, physicians, nurses, CCLS, caregivers, and patients will be blinded to which group the patient is randomized. The only person who will remain unblinded is the research coordinator.

The Vanderbilt Investigational Drug Service will provide the 1% Xylocaine MPF,saline vials, L.M.X.4 and placebo creams. The Investigational Drug Service will store, blind and dispense the creams and the J-Tip vials.

Tenotomy

On the day of the subject's tenotomy they will receive pain control based on their group assignment- L.M.X.4 cream (with J-Tip Saline) or J-Tip with 0.25mL of 1% Xylocaine MPF (with placebo cream). The treating physician will provide a Dimeglio score. The following procedures will take place:

- Baseline: FLACC and pulse ox data will be recorded as baby is positioned on treatment table
- Application of randomized topical cream (either L.M.X.4 or placebo cream) for 30 minutes timed.
- Peak FLACC and pulse ox data will be recorded within 5 seconds of application of LMX 4 or Placebo Cream
- Consent for tenotomy procedure will be obtained (routine care).
- Baseline #2: FLACC and pulse ox data will be recorded 30 minutes after cream application
- Parents will leave room (routine care).
- Patient stays with healthcare staff (Physician, nurse, CCLS, cast tech, trained research assistant)
- Cream will be removed from the subject's foot (routine care). Peak FLACC and Pulse Ox will be recorded within 5 seconds after cream removal.
- Baseline #3: FLACC and pulse ox data will be recorded 30 seconds after cream removal
- J-Tip injection with 1% Xylocaine MPF or saline. Peak FLACC scale measurements and pulse ox measurements will be recorded within 5 seconds of injection (1st foot if bilateral)
- Following J-Tip injection there will be a 3-minute break, baby will be calmed during this time.
- Baseline #4: FLACC scale measurements and pulse ox measurements 3 minutes after J-Tip injection
- Tenotomy will be performed
    - FLACC Scale data and Pulse Ox data will be measured during the following events:
        - Percutaneous incision for TAL (1st foot if bilateral)- Peak FLACC scale and Pulse Ox data will be recorded within 5 seconds of poke of scalpel
        - Start of casting, after cast padding placed (1st cast if bilateral)

- End of casting (2nd cast if bilateral)

Adverse local effects of the cream and/or J-Tip injection will be noted (skin redness, swelling, rash, etc). Procedural complications will be recorded (excessive bleeding, concern for neurovascular injury, etc).

Post-Tenotomy

REDCap Text Message Survey Collection
The subject's parents will receive a text or email message requesting they complete a REDCap survey 1, 7, 14, and 21 days after the tenotomy. They will be asked about the subject's pain level, irritability, doses of Tylenol administered, and any other problems that their child is having due to the procedure.

Clinical Visit around 21 days post-tenotomy (This visit is part of subject's routine care)
The subject will be assessed for complications. The treating physician will provide a Dimeglio score. A parental survey will be administered regarding quality of care, postoperative care, and perception of subject's pain level.

REDCap Survey questions to be sent to parents post TAL	
REDCap Survey Postop Day 1	1. On a scale of 1-5, with 1 being no pain and 5 being extreme pain, how much pain is your child having today due to the procedure? 2. On a scale of 1 to 5, with 1 being no irritability and 5 being extreme irritability, how irritable is your child today due to the procedure? 3. How many doses of Tylenol (acetaminophen) has your child been given today due to pain from the procedure? 4. If applicable, please list any other problems that your child is having today, due to the procedure.
REDCap Survey Postop Day 7, 14 & 21	1. On a scale of 1-5, with 1 being no pain and 5 being extreme pain, how much pain has your child had over the last week due to the procedure? 2. On a scale of 1 to 5, with 1 being no irritability and 5 being extreme irritability, how irritable has your child been over the last week due to the procedure? 3. On average, how many doses of Tylenol (acetaminophen) per day have been given to your child over the last week due to pain experienced from procedure? 4. If applicable, please list any other problems your child has had over the last week, due to the procedure.

Routine Care

All research activities will be conducted during routine care visits. The subject will not be asked to attend any research-only visits. Serial casting and the tenotomy procedure are routine care.

Standardizing the Environment

The environment the subject experiences during their weekly casting visits, the day of the tenotomy, and POD 21 will be standardized to ensure observed behaviors are due to the procedures taking place and not related to new stimuli. To standardize the environment the following will occur:

- CCLS will be present
- Casting by Moonlight (Turning off bright overhead lights, turning on small indirect light)
- Developmentally appropriate coping strategies, such as oral sucrose, music, soothing touch, and Tranquilo Vibration Mat, will be implemented upon CCLS, family, and or healthcare staff's discretion. The study is not limited to the following examples of coping strategies.

Schedule of Events

Study procedures	**Enrollment Visit**	**Weekly Casting Visits**	**Final Casting Visit (1 week prior to tenotomy)**	**Day of Tenotomy**	**POD1**	**POD7**	**POD14**	**POD 21**
Informed Consent	X							
Demographics	X							
Dimeglio Score	X			X (Prior to tenotomy)				X
FLACC Scale		X	X	X				
HR and O2 Levels via Pulse Ox		X	X	X				
CCLS Assessment of Temperament		X	X					
Randomization			X					
Parental Assessment of Temperament			X					
Application of J-Tip and L.M.X.4 Cream based on randomization assignment				X				
Parental REDCap Survey					X	X	X	X

Adverse Event/Complication Review				X				X

7.0 Risks

L.M.X.4 (4% Lidocaine) Topical Anesthetic Cream Risk

L.M.X.4 cream, is a topical anesthetic cream that may cause rash, redness, irritation, or swelling at the site of application. There is a risk that this drug may cause problems with heart rhythm.

J-Tip with 1% Xylocaine MPF Risks

Xylocaine may cause rash, redness, irritation, or swelling. There is a risk that this drug may cause problems with heart rhythm.

Breach of Confidentiality Risk:

During this study every attempt will be made to keep the patient's protected health information (PHI) private. Most study data will be maintained in a Vanderbilt REDCap database. Vanderbilt Redcap is a secure, web-based application for building and managing online databases. The data obtained and stored in Redcap will only be accessible by research personnel. Participating site, Texas Scottish Rite Hospital for Children, will be provided with access to the Vanderbilt REDCap database. The participating site will be able to view their records in the database but will not be able to view Vanderbilt's records. Any data sent to non-key study personnel for statistical analysis will be de-identified (dates will be shifted using a Redcap feature). Any physical study forms (ex. consent documents, surveys) will be kept in a locked cabinet in the principal investigator's office]. All study data will be maintained for 6 years following study completion. Following this 6 year period, the Redcap database will be archived and all physical study forms will be disposed of in shred-it confidentiality bins provided by VUMC.

Benefits

If it is determined that the utilization of the J-Tip system is equal to or more effective at reducing pain in infants undergoing a tenotomy than L.M.X.4 cream is, the potential benefits of this study may include better pain management in infants undergoing a tenotomy in the future. In addition, a reduction in the amount of time required to anesthetize the surgical area from 30 minutes with L.M.X.4 cream to 1-2 minutes with a J-Tip injection would decrease the overall length of the visit and cost of procedure, thus increasing quality, safety, and value.

8.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

The relationship of each adverse event to treatment rendered as judged by the investigator will be recorded on the Adverse Event Report Form. Due to the nature of the procedure involved in this study, certain adverse events may be considered normal sequalae associated with the procedure and will only be recorded if additional treatment is required or considered to be clinically significant. See specific indications for expected adverse events/complications due to nature of diagnosis.

Definitions

An AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Reporting Adverse Events

Any adverse event (clinical sign, symptom, or disease) temporally associated with the study treatment shall be documented in the adverse event (AE) CRF, except those events that are considered to be normal sequalae to the surgical procedure. All AE's meeting the above noted criteria are to be reported by the subject or observed by the Principal Investigator will be individually listed. The description of the event (confirmed diagnosis, if available), date of onset, date of resolution, action taken, severity and relationship to study treatment, and follow-up procedures will be reported.

The adverse event will be recorded in standard medical terminology. Additionally, the Principal Investigator will evaluate all adverse events as follows:

Action taken: whether or not the adverse event caused the subject to discontinue the study

Severity, to be assessed based on the table below:

AE Severity Description

DEGREE	DESCRIPTION
Mild (Grade 1)	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of the nature of subject.
Moderate (Grade 2)	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe (Grade 3)	Cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation

	of study participation; treatment for symptom(s) may be given and/or subject hospitalized
Life Threatening (Grade 4)	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care required.

Relationship to treatment to be graded as:

AE Relationship Description

RELATIONSHIP	DESCRIPTION
Not related	Any reaction that does not follow a reasonable temporal sequence from administration of the study treatment AND that is likely to have been produced by the subject's clinical state or other modes of therapy administered to the subject.
Unlikely	Any reaction that does not follow a reasonable temporal sequence from administration of the study treatment or that is likely to have been produced by the subject's clinical state or other modes of therapy administered to the subject.
Likely	A reaction that follows a reasonable temporal sequence from administration of the study treatment OR that follows a known response pattern to the suspected treatment AND that could not be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.
Definite	A reaction that follows a reasonable temporal sequence from administration of the study treatment AND that follows a known response pattern to the suspected treatment AND that recurs with rechallenge, and/or is improved by changing treatment

Serious Adverse Events (SAEs)

Events are classified as serious if they meet any of the following criteria (in accordance with 21 CFR 812.3(s)) and the recommendations of International Conference on Harmonization [Federal Register, October 7, 1997, Vol. 62, No. 194, pp 52239-45]):

i. Any death.
ii. Any life-threatening event, i.e., an event that places the subject, in the view of the investigator at immediate risk of death from the event as it occurred (does not include an event that, had it occurred in a more severe form, might have caused death).
iii. Any event that requires or prolongs in-patient hospitalization.
iv. Any event that results in persistent or significant disability/incapacity.
v. Any congenital anomaly/birth defect diagnosed in a child of a subject who participated in this study following the study procedure.

vi. Other medically important events that in the opinion of the investigator may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above.
vii. Any serious problem associated with the study treatment that relates to the rights, safety or welfare of study subjects.

The Principal Investigator or a member of the research staff will report all SAEs to the Institutional Review Board (IRB) according to the reporting requirements.

9.0 Study Withdrawal/Discontinuation

Participation in this study is voluntary. If at any time a study participant wishes to be withdrawn from the study, they may do so by contacting any of the key study personnel and letting them know they withdraw their consent. The date in which the participant withdraws their consent will be noted in their study file. Any information gathered up to the point of consent withdrawal may still be used for research and reporting.

Enrolled patients will be removed from the study if they are inconsistent with casting follow-up visits, noncompliant with treatment, or if the treating physician recommends TAL in the operating room due to specific patient factors, such as age or size.

10.0 Statistical Considerations

Power Analysis

A power analysis was conducted to determine the sample size needed to find a clinically meaningful difference of 2.5 point in the FLACC score (SD=3) between the two methods. With alpha=0.05, power=0.8, and and effect size d=.83, at least 24 patients per group are required (N=48). Assuming a 20% participant lost to follow-up rate, we will need to enroll 29 patients per group (N=58).

An interim power analysis was conducted to determine the sample size to find a clinically meaningful difference of 2.0 points in the FLACC score between the two methods. This was performed using the maximum SD of the FLACC score observations of the first 39 patients (SD=4.13). With alpha=0.05 and power=0.8, at least 47 patients per group are required (N=94).

Data Analysis

FLACC, heart rate, and oxygen saturation will be measured at 10 distinct time points (Table 1) during serial casting and following in-office TAL. Changes in FLACC score, heart rate, and oxygen saturation will be compared between treatment and control cohorts utilizing a two-way ANOVA with a Geisser-Greenhouse correction for matched time measures. A Sidak's multiple comparisons test will be utilized to assess differences between cohorts at each of the 10 time points assessed. To compare number of

complications between cohorts, data will be collected at 3-weeks post TAL and analyzed using a non-parametric Mann-Whitney test, given the ordinal nature of the data. Similar non-parametric analysis with correction for multiple comparisons between cohorts will be utilized to assess changes in responses to REDCap surveys. Statistical analysis will be conducted utilizing GraphPad Prism 8.3.0. Statistical significance will be $p<0.05$.

11.0 Privacy/Confidentiality Issues

During this study every attempt will be made to keep the patient's protected health information (PHI) private. Most study data will be maintained in a Vanderbilt REDCap database. Vanderbilt Redcap is a secure, web-based application for building and managing online databases. The data obtained and stored in Redcap will only be accessible by research personnel. Participating site, Texas Scottish Rite Hospital for Children, will be provided with access to the Vanderbilt REDCap database. The participating site will be able to view their records in the database but will not be able to view Vanderbilt's records. Any data sent to non-key study personnel for statistical analysis will be de-identified (dates will be shifted using a Redcap feature). Study personnel will use VUMC Box to share research documents. The VUMC Box study folder will only be accessible by research personnel. Any physical study forms (ex. consent documents, case report forms) will be kept in a locked cabinet in the principal investigator's office. All study data will be maintained for 6 years following study completion. Following this 6-year period, the Redcap database will be archived and all physical study forms will be disposed of in shred-it confidentiality bins provided by VUMC.

12.0 Follow-up and Record Retention

The duration of this study will last until we have enrolled and completed follow-up on 24 patients per group (N=48). All study data will be maintained for 6 years following study completion. Following this 6 year period, the Redcap database will be archived and all physical study forms will be disposed of in shred-it confidentiality bins provided by VUMC.

13.0 References

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14.0 Temperament Assessment Evidence

"The Origin of Personality" by Thomas, Chess and Birch, 1970.

- "Infants begin to express themselves as individuals from the time of birth."
- "[Thomas, Chess, & Birch] identified nine characteristics that could be reliably scored on a three point scale (medium, high and low). The set of ratings in these nine characteristics defines the temperament, or behavioral profile, of a child, and the profile is discernible even as early as the age of two or three months."
- "Children do show distinct individuality in temperament in the first weeks of life, independently of their parents' handling or personality style. Our long term study has now established that the original characteristics of temperament tend to persist in most children over the years."

- "[Thomas, Chess, & Birch] found that certain characteristics did cluster together and defined three general types of temperament: easy, difficult, and slow to warm up."
- "Behavior of a child reveals that he has a distinct temperament early in life. These reports taken from interviews with the parents of the children studied by the authors show that temperamental differences are apparent when a child is only two months old."
- Temperamental characteristics that are crucial to classifying a child as easy, slow to warm up, and difficult are rhythmicity, approach/ withdrawal, adaptability, intensity of reaction, and quality of mood." ((we also included threshold of responsiveness))
- **We will take 6 of the 9 characteristic stages, including each of the 5 crucial characteristics, for our study. Results will be broken into subgroups

15.0 FLACC Evidence

"Clinical Validation of FLACC: Preverbal Patient Pain Scale" by Manworren & Hynan, (2003)

- Pediatric nurses used the FLACC scale to assess pain in 147 children under 3 years of age who were hospitalized in the pediatric intensive care unit, post-anesthesia care unit, surgical/ trauma unit, hematology/ oncology unit, or infant unit. FLACC is an observational tool for quantifying pain behaviors. Facial expression, leg movement, activity, cry, and consolability are each scored 0-2 for a total FLACC score of 0-10. The FLACC measurements were done pre-analgesia, at predicted onset of analgesia, and at predicted peak analgesia.
- This study found that the FLACC pain assessment tool is appropriate for preverbal children in pain from surgery, trauma, cancer, or other disease processes. The results support pediatric nurses' clinical judgement to determine analgesic choice rather than providing distinct FLACC scores to guide analgesic selection.
- This is the FLACC Scale. We will be measuring "Face, Legs, Activity, Cry and Consolability" https://journals.lww.com/ajnonline/fulltext/2002/10000/pain_assessment_in_infants_and_young_children__the.24.aspx?casa_token=vHoSGXsRSCQAAAAA:g5nV_LfIBDURPC5A_3WdRI1_sNt1-MfkyoQFWaqUjASHwfKHTiXftxU-LCWSrW5kVgtC0ZL7JvAvgI-QRj4b6Os

	Scoring		
Categories	O	1	2
Face	No particular expression or smile.	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to; distractable	Difficult to console or comfort

Note: Each of the five categories Face (F), Legs (L), Activity (A), Cry (C), and Consolability (C) is scored from 0-2, which results in a total score between 0 and 10.
From Merkel, Voepel-Lewis, Shayevitz, & Malviya (1997). The FLACC: A behavioral scale for scoring postoperative pain in young children.
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