Prospective, Randomized, Double-blinded, Split-face Study Comparing Efficacy of Lidocaine 2.5%/Prilocaine 2.5% Cream Under Occlusion, and Compounded Lidocaine 23% /Tetracaine 7% Ointment for Topical Anesthesia Prior to 1927 nm Fractional Thulium Fiber Laser Treatment of the Face

NCT04523961

22February2021

IRB Minimal Risk Protocol Template

Note: If this study establishes a human specimen repository (biobank) for research purposes, do not use this template. Use the Mayo Clinic Human Specimen Repository Protocol Template found on the IRB home page under Forms and Procedures at http://intranet.mayo.edu/charlie/irb/

First-time Use: Use this template to describe your study for a new IRB submission.

1. Complete the questions that apply to your study.
2. Save an electronic copy of this protocol for future revisions.
3. When completing your IRBe application, you will be asked to upload this document to the protocol section.

Modification: To modify this document after your study has been approved:

1. Open your study in IRBe. Click on the study 'Documents' tab and select the most recent version of the protocol. Save it to your files.
2. Open the saved document and activate "Track Changes".
3. Revise the protocol template to reflect the modification points , save the template to your files
4. Create an IRBe Modification for the study and upload the revised protocol template.

General Study Information

Principal Investigator: Dr. Elika Hoss

Study Title: Prospective, randomized, double blinded, split-face study comparing efficacy of lidocaine 2.5%/ prilocaine 2.5% cream under occlusion and compounded lidocaine 23% / tetracaine 7% ointment for topical anesthesia prior to 1927 nm fractional thulium fiber laser treatment of the face

Protocol version number and date: 3, 2/22/2021

Research Question and Aims

Hypothesis: Does lidocaine 23% / tetracaine 7% ointment provide greater topical anesthetic compared to lidocaine 2.5%/ prilocaine 2.5% cream?

Aims, purpose, or objectives:

1. To compare the efficacy of lidocaine 23% / tetracaine 7% ointment and lidocaine 2.5%/ prilocaine 2.5% cream in reducing self-reported pain after laser treatment.
2. To determine the amount of burning and itching a patient experiences with lidocaine 23% / tetracaine 7% ointment compared to lidocaine 2.5%/ prilocaine 2.5% cream.
3. To determine if any symptoms of lidocaine toxicity occur during treatment visit (tinnitus, lightheadedness, diplopia, metallic taste in the mouth, slurred speech, localized muscle twitching, fine tremors).
4. To determine the amount of erythema on the face after application of both anesthetics.

Background (*Include relevant experience, gaps in current knowledge, preliminary data, etc*.):

Topical anesthetics are used commonly in outpatient dermatologic procedures. Applied topical anesthetics must transverse the epidermis and target the nerves in the dermis. Occlusion is one of several techniques that help with dermal absorption of the topical anesthetic[1]. Topical anesthetic is not without risk. Signs and symptoms of lidocaine toxicity can start around blood lidocaine levels of 1-5 μg/mL and respiratory depression and/or coma at 20-25 μg/mL.

A commonly used FDA-approved medication for topical anesthetic is EMLA ® Cream, a eutectic mixture of lidocaine 2.5% and prilocaine 2.5%. EMLA ® Cream is applied to intact skin under occlusive dressing for at least 1 hour, with maximum dermal analgesia at 2-3 hours[2]. The amount systemically absorbed is related to the surface area that it is applied and the duration of time applied. When applied to over 400 cm^2 for 24 hours, the peak blood levels of lidocaine was approximately 1/20 of the systemic toxic level and prilocaine was approximately 1/36 the toxic level.

Higher levels of lidocaine have also shown to be safe. A prospective study of lidocaine 30% was shown to be well tolerated with no adverse reaction when used on the face, neck, and chest with intense pulse light treatment[3]. In another study, 12 grams of 23% lidocaine/7% tetracaine ointment was applied to face for 2 hours, and the median peak lidocaine level was 1.15 μg/mL with no serious adverse effects. Twenty-one percent of patients reported a symptom of dizziness, drowsiness, lightheadedness, numbness or tingling, or back pain, and 90% of patients reported at least one cutaneous side effect [4].

Absorption of lidocaine has been well studied[2]. When applying 2.5% lidocaine to intact skin, 0.045 mg/cm^2 of lidocaine is absorbed per hour. At 12 times the strength, 30% lidocaine cream would then absorb 0.54 mg/cm^2/hour. Assuming the full face was covered at 300 cm^2 for one hour, the total lidocaine absorbed would be 121.5 mg (0.54*300*1.0) would be 162 mg. The maximum recommended dose of lidocaine without epinephrine is 4.5 mg/kg or 300 mg. For example, a low weight patient (50 kg) patient would have a maximum of dose of 225 mg.

EMLA ® Cream is the only FDA approved topical anesthetic available for dermatologic outpatient procedures, however, use of other topical anesthetics is common and there is limited data comparing the efficacies. We aim to compare the efficacy of lidocaine 2.5%/prilocaine 2.5% cream under occlusion and compounded lidocaine 23% / tetracaine 7% ointment for topical anesthesia prior to 1927 nm fractional thulium fiber laser treatment of the face.

Study Design and Methods

Methods:

Lidocaine 23% / tetracaine 7% ointment and lidocaine 2.5%/ prilocaine 2.5% cream are both topical anesthetics that are used commonly by cosmetic dermatologists to numb the skin prior to laser procedures. We want to perform a prospective study evaluating the amount of pain (10 point VAS score for pain), burning, and itching that patients experience during the procedure. The targeted patients for accrual will be patients paying to undergo 1927 nm fractional thulium fiber laser treatment of the face for photodamage. Patients will be recruited between approval of IRB modification until we obtain target accrual, estimated to go until 12/2021.

Prior to the procedure, we will obtain consent from the patient to participate in the study. Lidocaine and tetracaine are pregnancy category B and thus pregnancy test is not needed if patients meet definitions described in inclusion criteria. Valacyclovir 500mg twice daily for 10 days will be given to all patients with a history of cold sores. We will randomly assign half of the face to be applied with 2.5 g of lidocaine 23% / tetracaine 7% ointment without occlusion and the other half of the face with 7.5 g lidocaine 2.5%/ prilocaine 2.5% cream with occlusion for 60 minutes compounded by Mayo Clinic Pharmacy. The topical anesthetics will only be applied to intact skin that is at least 1 cm away from the eyes. Lidocaine 2.5%/ prilocaine 2.5% cream will be applied to half the face by nursing staff and occluded. Lidocaine 23% / tetracaine 7% ointment will be applied to the other half of the face by the patient, given that it is their own outside prescription.

After 60 minutes we will remove the creams with soap and water, cleanse face with alcohol to ensure face is free of all moisture and water. Before the procedure, patients will take an electronic RedCap survey on an iPad to determine burning and itching on each side of the face. Physicians will assess erythema on each side of the face. Next, we will measure the surface area of the face with one Fraxel 1927nm nonablative fractionated laser treatment and treat the face with a fluence of 20 mJ and treatment level of 7-11. The following areas will be treated in this order: right forehead, left forehead, left cheek, right cheek, nose, perioral area. After the procedure, we will have them take an electronic RedCap survey on an iPad to determine pain associated with procedure. The physician will also assess for systemic symptoms of lidocaine toxicity. Then, the patient will apply triamcinolone 0.1% ointment for 1 week with vinegar soaks, vaniply, and gentle skin care.

As part of the division of dermatologic surgery procedure protocol, patient will be contacted on post procedure day 1. They will be asked how they are doing, if they have any questions about wound care instructions, pain or blistering as part of standard procedure. Then, in addition to that, we will ask their 1 hour post procedure pain level on a scale of 1-10 for each side of the face”

The following is a patient (70kg female) scenario to ensure safe levels of lidocaine.

We will assume a facial surface area of 300 cm^2. If half of that (150 cm^2) is covered with 7.5 mg lidocaine 2.5%/ prilocaine 2.5% (EMLA Cream) under occlusion for 60 minutes, the lidocaine absorption would be (0.045*150*1) 6.75 mg. The other half of the face would be covered with 2.5 g of Lidocaine 23% / tetracaine 7% ointment, which would cause around 62.1 mg of lidocaine to be absorbed (0.414*150*1). If she was 70 kg, this would be well under the maximum dose (315 mg).

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Subject Information

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Target accrual: 32

Subject population (children, adults, groups): Adults

Inclusion Criteria:

a. Male or Female in general good health 18 years of age or older undergoing fraxel laser treatment
b. Fitzpatrick skin type I-IV with at least mild photodamage of the face by physician discretion
c. Subject has completed an appropriately administered informed consent process which includes signing the IRB approved consent form
d. Willingness to have facial exams and digital photos performed of the face
e. Female patients will be either of non-childbearing potential defined as:
    1. Having no uterus
    2. No menses for at least 12 months.

    Or;

    (WOCBP) women of childbearing potential must agree to use an effective method of birth control during the course of the study, such as:
    1. Oral contraceptive pill, injection, implant, patch, vaginal ring, intrauterine device
    2. Intrauterine coil
    3. Bilateral tubal ligation
    4. Barrier method used with an additional form of contraception (e.g., sponge, spermicide or condom)
    5. Abstinence (If practicing abstinence must agree to use barrier method described above (4) if becomes sexually active).
    6. Vasectomized partner (Must agree to use barrier method described above (4) if becomes sexually active with non-vasectomized).

Exclusion Criteria:

a. Presence of incompletely healed wound or active skin disease within in treatment area
b. Pregnant, planning pregnancy or breastfeeding during the course of the study
c. Individuals who have ablative laser within 6 months; non ablative lasers, facial peels, or dermabrasion within 1 month
d. Individuals with known allergies or sensitivities to any of the ingredients of any topical products being used in this study (a list of the products with active and excipients will be provided below)
e. Subjects with any pre-existing medical or psychological condition which, in the opinion of the investigator, would put them at increased risk due to study treatment or participation
f. Subjects who are unable to comprehend the study consent document or provide full written consent

g. Subjects who have taken isotretinoin within 3 months or systemic corticosteroids within 1 month.
h. Subjects with history of severe cardiovascular disease, kidney disease, liver disease, uncontrolled diabetes, uncontrolled seizures, immunosuppression.

Biospecimens

There will be no collection of biospecimens

Review of medical records, images, specimens

Check all that apply (data includes medical records, images, specimens).

☐ Only data that exists before the IRB submission date will be collected.

Date Range for Specimens and/or Review of Medical Records:
Examples: *01/01/1999 through 12/31/2015*, or all records through *mm/dd/yyyy*.

Note: The Date Range must include the period for collection of baseline data, as well as follow-up data, if applicable.

☒ The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.
Examples

- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

Data Analysis

Power Statement: Assuming a mean of paired differences of 1.25 on the VAS, a standard deviation of paired differences of 2.3, and a significance level of 5%, we would need 32 patients to achieve at least 80% power using a two-sided paired t-test.

Data Analysis Plan: The mean pain scale from each topical anesthetic will be compared using t-tests.

Endpoints
Primary: To compare the efficacy of lidocaine 23% / tetracaine 7% ointment and lidocaine 2.5%/ prilocaine 2.5% cream in reducing self-reported pain after laser treatment.
Secondary: To determine if there is difference in burning and itching after use of lidocaine 23% / tetracaine 7% ointment and lidocaine 2.5%/ prilocaine 2.5% cream; To determine if there are any systemic symptoms or any difference in erythema after use of lidocaine 23% / tetracaine 7% ointment and lidocaine 2.5%/ prilocaine 2.5% cream.

References:

1. Liu DR, Kirchner HL, Petrack EM. Does using heat with eutectic mixture of local anesthetic cream shorten analgesic onset time? A randomized, placebo-controlled trial. *Ann Emerg Med.* 2003;42(1):27-33.
2. Astra Pharmaceutical Production, AB Astra Pharmaceuticals, L.P. EMLA Cream [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/019941s021lbl.pdf. Accessed March 18th, 2020.
3. Humphrey S, Carruthers A. Safety of Lidocaine 30% in a Plasticized Base as Local Anesthesia for Intense Pulsed Light Treatment. *Dermatol Surg.* 2019;45(5):752-756.
4. McCleskey PE, Patel SM, Mansalis KA, Elam AL, Kinsley TR. Serum lidocaine levels and cutaneous side effects after application of 23% lidocaine 7% tetracaine ointment to the face. *Dermatol Surg.* 2013;39(1 Pt 1):82-91.