TITLE: Characterizing and Comparing the Duration of Local Anesthetic in Dermatologic Surgery

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Statement of Compliance

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM, unless disclosure on ClinicalTrials.gov is federally required.

Weill Cornell Medicine

Institution Name

Kira Minkis, MD, PhD

Principal Investigator's Name

List of Abbreviations

AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
CTSC	Clinical Translational Science Center
DSMP	Data Safety Monitoring Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
WCM	Weill Cornell Medicine

Summary of Changes (Protocol Version Date 4-7-2024):

This amended protocol includes language to clarify that data from the fourth cohort (added in the previous amended protocol) will be analyzed separately from the data collected from the first three cohorts.

Language to this effect has been added to the protocol in relevant sections (all changes in red):

Page # 13: Study design, overall design. We have included the following text, “Data from this fourth cohort, which will compare two doses of the same anesthetic, will be analyzed separately from the data collected from cohorts 1-3.”

Page # 14: Table 2. In reviewing the protocol, we found a typo in Table 2 on page 14. The comparison within for the fourth cohort is between two doses (0.5 ml and 1.0ml) of Lidocaine+epinephrine, not Ropivacaine as was erroneously included in the previous version.

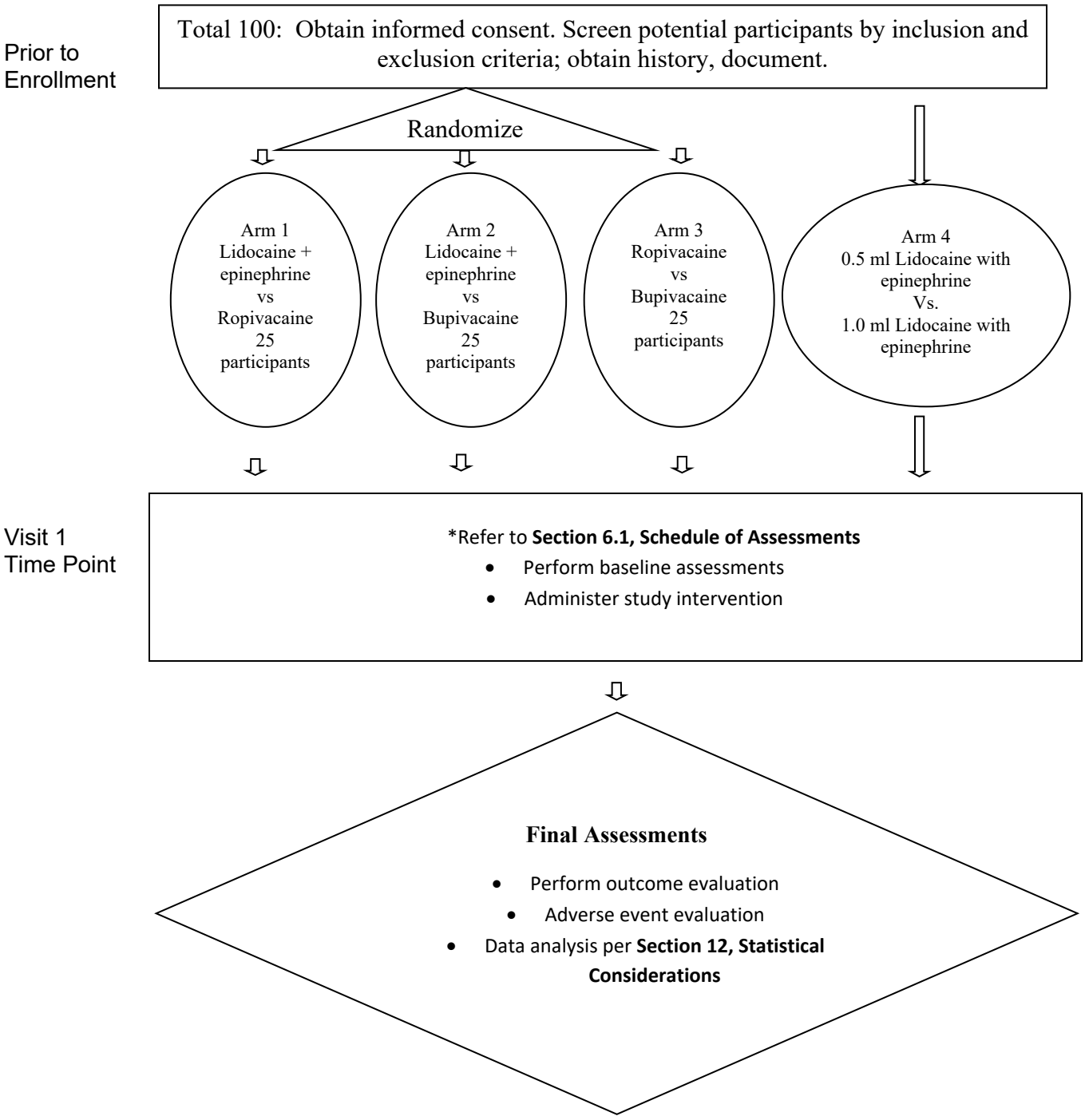
1. Protocol Summary

Full Title:	Characterizing and Comparing the Duration of Local Anesthetic in Dermatologic Surgery
Short Title:	Split Face Study of the Duration of Local Anesthetics
Principal Investigator:	Kira Minkis MD, PhD
Study Description:	This study will allow us to compare the relative durations of local anesthetics within the same subject at a highly vascularized anatomic region of skin, the nasal ala. We will test and compare the relative durations and efficacy of commonly used long acting (ropivacaine or bupivacaine) and short acting local anesthetics (lidocaine with epinephrine), delivered via local anesthesia. We will use a modification of a previously published approach of non-invasive pinprick testing to assess the duration of local anesthetic. We hypothesize that the duration of anesthesia of short-acting anesthetics will not differ significantly from long-acting anesthetics at a single site and there will not be a significant difference between the two long-acting anesthetics at a single site. Additionally, we will investigate the role of anesthetic volume on the duration of action at highly vascular sites.
Sample Size:	N=100 patients total (N=25 in each of the following cohorts comparing local anesthetics: 1) lidocaine + epinephrine vs. ropivacaine, 2) lidocaine + epinephrine vs. bupivacaine, 3) ropivacaine vs. bupivacaine, 4) 0.5 ml lidocaine with epinephrine vs 1.0 ml lidocaine with epinephrine)
Enrollment:	This study will enroll up to 100 subjects and screen up to 125 subjects.
Study Population:	Volunteers over the age of 18 will be included in the study. Volunteers under age of 18, those with previous adverse reactions to local anesthetics, those who are pregnant, those with altered mental status or those with a history of peripheral vascular disease or known diseases affecting nerve function will be excluded from the study.
Enrollment Period:	We anticipate it will take approximately 18 months to enroll the subjects.
Study Design:	Eligible participants will be randomized to receive two different local anesthetics (or two different volumes of the same local anesthetic) to be administered to both sides of the nose. See Table 2 for the sequential cohorts to be enrolled. The dermatologic surgeon/PI (Dr. Kira Minkis, MD, PhD) will administer the local anesthetic. We will assay the duration of local anesthetic at 15-minute increments using a modification of the previously published non-invasive pinprick testing. The co-investigator and participant will be blinded to the side (left or right) to which each anesthetic (or volume of the same local anesthetic) is injected.

Description of Sites/ Facilities Enrolling Participants:	This is a single-site study at the Department of Dermatology at Weill Cornell Medicine.
Study Duration:	The study should take approximately 18 months to complete. In summary, 6 months will be needed for patient recruitment and study completion, and 12 months for data analysis and manuscript preparation/peer review process.
Participant Duration:	It will take 1 visit for each patient to complete the study. Each visit will last approximately 3-4 hours.
Primary Objective:	To compare the duration of commonly used local anesthetics in dermatologic surgery, including lidocaine + epinephrine, ropivacaine and bupivacaine, as well as two different volumes of the same local anesthetic, lidocaine with epinephrine, delivered subcutaneously at the nasal ala.
Secondary Objectives:	To correlate patient demographics (including age, BMI, gender, hair color and co-morbidities) with the relative duration of different local anesthetics.
Exploratory Objectives:	*N/A*
Primary Endpoints:	The primary endpoint will be the time to return to baseline sensation (in minutes), as measured by a modification of the previously published non-invasive pin-prick testing method, and recorded by the questionnaire.
Secondary Endpoints:	None

1.1 Schema

Figure 1: Flow Diagram



1.2 Study Objectives and End Points

The purpose of this study is to investigate how the duration of local anesthetics differ when administered to areas of skin with high vascularity during dermatologic surgery.

1.2.1 Primary Objectives

To compare the relative duration of commonly used local anesthetics (lidocaine + epinephrine, ropivacaine and bupivacaine) as well as different volumes of the same local anesthetic, lidocaine with epinephrine, delivered subcutaneously at the nasal ala.

1.2.2 Secondary Objectives

To correlate patient demographics (including age, BMI, gender, hair color and co-morbidities) with the relative duration of different local anesthetics.

1.2.3 Exploratory Objectives

None

1.2.4 Primary Endpoints

The primary endpoint will be the time to return to baseline sensation, as measured by a modification of the previously published non-invasive pin-prick testing method, and recorded by the questionnaire.

1.2.5 Secondary Endpoints

None

2. Background

2.1 Disease

None

2.2 Investigational Agent/Device, or Surgical Treatment/Method

The interventional agents used in this study include 3 commonly used local anesthetics– lidocaine with epinephrine, ropivacaine, and bupivacaine (brand name Marcaine). These agents will be utilized in applications consistent with standard of care in dermatologic surgery and many procedures across various disciplines of medical care. All 3 anesthetics are FDA approved for use as local anesthetics, therefore, are being used on-label. These applications are well studied, allowing investigators to understand their efficacy and other drug properties to be outlined in this section. No changes are anticipated in the agents used in this study.

Xylocaine with epinephrine (lidocaine with epinephrine)(1)

Mechanism of action:

Lidocaine HCL stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses thereby effecting local anesthetic function.

Major route of elimination:

Lidocaine crosses the blood-brain barrier and placental barriers, possibly through passive diffusion and is rapidly metabolized by the liver. Both metabolites and unchanged drug are metabolized by the liver.

Safety profile:

Lidocaine has a good safety profile. Toxicity is determined by both total dose (usually 6-7 mg/kg) and rate of absorption, which depends on local tissue blood flow and the use of vasoconstrictors such as epinephrine.(2) See section 2.4.1 Known Potential Risks for an overview.

Potential for drug interactions:

There are clinically significant drug interactions. Administration of local anesthetics with epinephrine to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe prolonged hypertension. Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine. Concurrent administration of vasopressors and ergot-type oxytocic drugs may cause severe persistent hypertension or cerebrovascular accidents.

Lidocaine should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics, since the toxic effects of these drugs are additive. Cytochrome P4501A2 is involved in the formation of 3-hydroxy ropivacaine, the major metabolite. In vivo, the plasma clearance of ropivacaine was reduced by 70% during coadministration of fluvoxamine (25 mg bid for 2 days), a selective and potent CYP1A2 inhibitor. Thus strong inhibitors of cytochrome P4501A2, such as fluvoxamine, given concomitantly during administration of Naropin, can interact with Naropin leading to increased ropivacaine plasma levels. Caution should be exercised when CYP1A2 inhibitors are coadministered. Possible interactions with drugs known to be metabolized by CYP1A2 via competitive inhibition such as theophylline and imipramine may also occur. Coadministration of a selective and potent inhibitor of CYP3A4, ketoconazole (100 mg bid for 2 days with ropivacaine infusion administered 1 hour after ketoconazole) caused a 15% reduction in in vivo plasma clearance of ropivacaine. Patients who are administered local anesthetics are at increased risk of developing methemoglobinemia when concurrently exposed to the following drugs, which could include other local anesthetics: articaine, benzocaine, bupivacaine, lidocaine, mepivacaine, prilocaine, procaine, ropivacaine, tetracaine.

Rationale for the starting dose and regimen chosen:

We plan to use a minimal effective dose of 0.5mL of 1% lidocaine with epinephrine 1:100,000 as well as 1.0 ml of 1% lidocaine with epinephrine, a common dose for local anesthesia, in addition to local anesthesia required for the Mohs surgery.

Marcaine (bupivacaine)(3)

Mechanism of action:

Bupivacaine is related chemically and pharmacologically to the aminoacyl local anesthetics. It is a homologue of mepivacaine and is chemically related to lidocaine. All three of these anesthetics contain an amide linkage between the aromatic nucleus and the amino, or piperidine group. They differ in this respect from the procaine-type local anesthetics, which have an ester linkage. Bupivacaine blocks the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

Major route of elimination:

Amide-type local anesthetics such as bupivacaine are metabolized by the liver and excreted via the kidneys.

Safety profile:

The maximum single infiltration dose of bupivacaine is 2.5-3mg/kg.(2)

See section 2.4.1 Known Potential Risks for an overview.

Potential for drug interactions:

Bupivacaine should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics, since the toxic effects of these drugs are additive. Cytochrome P4501A2 is involved in the formation of 3-hydroxy ropivacaine, the major metabolite. In vivo, the plasma clearance of ropivacaine was reduced by 70% during coadministration of fluvoxamine (25 mg bid for 2 days), a selective and potent CYP1A2 inhibitor. Thus strong inhibitors of cytochrome P4501A2, such as fluvoxamine, given concomitantly during administration of Naropin, can interact with Naropin leading to increased ropivacaine plasma levels. Caution should be exercised when CYP1A2 inhibitors are coadministered. Possible interactions with drugs known to be metabolized by CYP1A2 via competitive inhibition such as theophylline and imipramine may also occur. Coadministration of a selective and potent inhibitor of CYP3A4, ketoconazole (100 mg bid for 2 days with ropivacaine infusion administered 1 hour after ketoconazole) caused a 15% reduction in in vivo plasma clearance of ropivacaine. Patients who are administered local anesthetics are at increased risk of developing methemoglobinemia when concurrently exposed to the following drugs, which could include other local anesthetics: articaine, benzocaine, bupivacaine, lidocaine, mepivacaine, prilocaine, procaine, ropivacaine, tetracaine.

Rationale for the starting dose and regimen chosen:

We plan to use a minimal effective dose of 0.5mL of 0.5% Marcaine (bupivacaine) in addition to local anesthesia required for the Mohs surgery.

Naropin (ropivacaine)(4)

Mechanism of action:

Ropivacaine is a member of the amino amide class of local anesthetics and is supplied as the pure S-(-)-enantiomer. Ropivacaine blocks the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise

of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

Major route of elimination:

Metabolized by the liver and excreted via the kidneys.

Safety profile:

The maximum single infiltration dose of ropivacaine is 3-4 mg/kg.(2)

See section 2.4.1 Known Potential Risks for an overview.

Potential for drug interactions:

Ropivacaine should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics, since the toxic effects of these drugs are additive. Cytochrome P4501A2 is involved in the formation of 3-hydroxy ropivacaine, the major metabolite. In vivo, the plasma clearance of ropivacaine was reduced by 70% during coadministration of fluvoxamine (25 mg bid for 2 days), a selective and potent CYP1A2 inhibitor. Thus strong inhibitors of cytochrome P4501A2, such as fluvoxamine, given concomitantly during administration of Naropin, can interact with Naropin leading to increased ropivacaine plasma levels. Caution should be exercised when CYP1A2 inhibitors are coadministered. Possible interactions with drugs known to be metabolized by CYP1A2 via competitive inhibition such as theophylline and imipramine may also occur. Coadministration of a selective and potent inhibitor of CYP3A4, ketoconazole (100 mg bid for 2 days with ropivacaine infusion administered 1 hour after ketoconazole) caused a 15% reduction in in vivo plasma clearance of ropivacaine. Patients who are administered local anesthetics are at increased risk of developing methemoglobinemia when concurrently exposed to the following drugs, which could include other local anesthetics: articaine, benzocaine, bupivacaine, lidocaine, mepivacaine, prilocaine, procaine, ropivacaine, tetracaine.

Rationale for the starting dose and regimen chosen:

We plan to use a minimal effective dose of 0.5mL of 0.5% ropivacaine in addition to local anesthesia required for the Mohs surgery.

2.3 Rationale

Unlike other types of surgeries, patients undergoing dermatologic surgery are conscious and awake throughout the procedure. Perioperative anxiety, as can be caused by inadequate pain control, can lead to increased risk of surgical complications, including intraoperative and postoperative bleeding. Therefore, it is critical for physicians to minimize pain levels in order to maximize patient comfort throughout the surgery. While the time of onset and duration of local anesthetics is well defined, few studies to date have examined how different anatomical areas influence the duration of local anesthesia or how combination of different local anesthetics influences duration of anesthesia. Earlier work completed by our research team (now in pre-publication) has revealed clinically relevant differences in duration of both long and short acting local anesthetics between regions that differ in cutaneous vascularity.

We conducted two prospective observational studies of patients undergoing Mohs surgery at a single academic institution. Patients with a history of adverse reactions to local anesthesia, peripheral vascular disease, neuropathy, or other impairment in nerve function were excluded. Patients less than 18 years old of age and those that were pregnant or breastfeeding were also excluded. Demographic and clinical information was collected. Baseline anxiety was recorded using the visual analog scale for anxiety (VAS-A). The nose and the shin were chosen to represent highly and poorly vascularized anatomic sites, respectively. Participants were anesthetized at each site with a subcutaneous injection of either 0.5 mL of buffered lidocaine 1% + epinephrine 1:100,000 for our first study or 0.5 mL of 0.2% ropivacaine for our second study. Sensation was determined by pinprick prior to injection, at baseline, and every 15 minutes until sensation returned or surgery concluded. The primary endpoint was time to return of pinprick sensation.

Our initial study utilizing lidocaine enrolled 25 patients. The mean age of the study cohort was 68 years (range 23-95) with 15 men and 10 women. The duration of anesthesia was significantly shorter on the nose compared to the shin ($p<0.0001$). On the nose, there was an association between gender and duration of anesthesia. There was no correlation between baseline anxiety score, age, BMI, and duration of local anesthesia.

Our second study utilizing ropivacaine recruited 29 patients. The median age was 71.5 years (range 46-89) with 17 women and 12 men. The median duration of ropivacaine was 60.0 minutes (45.0, 60.0) on the nose and 210.0 minutes (165.0, NA) on the shin. 22 of 29 (75.9%) participants did not regain sensation on the shin by study end, therefore the median duration was underestimated, and the upper quartile was unable to be determined. As shown in Figure 1, the Kaplan-Meier survival curve indicated that the duration of ropivacaine was higher at the shin than the nose (log-rank test, $\chi2=56.96$; $P<.0001$). The percentage of subjects that regained sensation within 1-hour was 75.9% on the nose vs. 3.5% on the shin ($\chi2=21.00$, $p<0.0001$). Participants with history of hypertension were more likely to regain sensation on the nose by 60 minutes, though this did not achieve statistical significance (OR 6.16; 95% CI, 0.81 to 46.76; $p=.079$). Comorbidities including underlying anxiety/depression, diabetes, and kidney disease did not significantly impact duration of ropivacaine action on the nose.

Our results suggest that the duration of subcutaneous lidocaine + epinephrine and ropivacaine vary by anatomic region. We hypothesize that differences in vascularity of the nose and the shin contributes to these results. The duration of anesthesia was shorter in highly vascularized regions such as the nose, compared to less vascularized regions such as the shin. This study emphasizes a potential gap in effective pain control during dermatologic surgery, but also an opportunity to intervene to improve our patients' surgical experience.

Given these findings, it is crucial that we now specifically compare reportedly long-acting and short acting anesthetics in highly vascularized tissue of anatomic regions commonly operated on by dermatologic surgeons. Furthermore, we will compare two different volumes of a single long-acting anesthetic (lidocaine with epinephrine) to determine the role that the quantity of anesthetic injected may play in duration of action in this area of particularly high vascularity. In such highly vascularized tissue, adjuvant use of reported long-acting anesthetics (or increased volume of anesthetic) may not confer additional benefit over a widely available and more cost effective short-acting lidocaine solution.

Adjuvant use of a long-acting anesthetic such as bupivacaine to prolong anesthesia is common with the intention to provide relief from multiple injections of shorter-acting lidocaine.(5) Additionally, pain is frequently reported on postoperative days 0 to 3, leading some to recommend the use of long-acting local anesthetics to prevent over-prescription or a gap in pain coverage.(6, 7) Adequate pain management both during and after surgery may improve recovery, hasten patient mobilization, and reduce postoperative complications. However, long-acting anesthetics such as the commonly used bupivacaine are costly, with 50 milliliters of 0.5%

injectable solution costing $66.19. By comparison, 500 milliliters of 1:100000-1% epinephrine/lidocaine injectable solution costs $64.57.(8) Further, patients may actually experience shorter than expected anesthesia. In a double-blinded randomized block design of 25 subjects, Collins et al reported no difference in the duration of anesthesia on the forearm between lidocaine + epinephrine, bupivacaine + epinephrine, and 2 mixtures of bupivacaine and lidocaine + epinephrine.(9)

The split-face design of this proposed study serves the role of advancing our understanding of a common clinical practice in dermatologic surgery. Split-face design has been used widely in dermatological surgery research to answer a diverse set of topics from injectable associated pain to the efficacy of jawline augmentation techniques.(10, 11) Similarly, split-scar studies have been utilized to evaluate different closure techniques of a single defect.(12) With this approach, two different anesthetics will be administered to different sides of the body in the same subject. For example, short acting lidocaine may be injected subcutaneously to the right side of the nose, while long-acting bupivacaine is injected to the left side of the nose. This approach allows us to compare these local anesthetics.

Despite advances in our understanding of mechanisms of action of local anesthetics and their application to outpatient surgeries, to date, there have been no studies evaluating how the duration of different anesthetics compare to one another when administered to skin with high vascularity. Based on the aforementioned studies and our own experience, we hypothesize that given the highly vascularized nature of the face and hand, the duration of long-acting anesthetics (ropivacaine or bupivacaine) will not differ significantly from the duration of short-acting anesthetics (lidocaine ± epinephrine). Further, we hypothesize that the duration of ropivacaine will not differ significantly from bupivacaine, two different long-acting anesthetics with different reported durations of action. Defining the duration of local anesthetic based on anatomical regions will help guide better practice management, safe use of anesthesia and adequate pain control for patients undergoing dermatologic procedures.

2.4 Risk/Benefit Assessment

2.4.1 Known Potential Risks

Xylocaine with epinephrine (lidocaine with epinephrine)(1)

- WARNINGS: XYLOCAINE INJECTIONS FOR INFILTRATION AND NERVE BLOCK SHOULD BE EMPLOYED ONLY BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES THAT MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED AND THEN ONLY AFTER ENSURING THE IMMEDIATE AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY EQUIPMENT AND THE PERSONNEL NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES. (See also ADVERSE REACTIONS and PRECAUTIONS.) DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.

- Xylocaine with epinephrine solutions contain sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people. For more information on Precautions, please see cited package insert.

Marcaine (bupivacaine)(3)

- MARCAINE is contraindicated in patients with a known hypersensitivity to it or to any local anesthetic agent of the amide-type or to other components of MARCAINE solutions.
- LOCAL ANESTHETICS SHOULD ONLY BE EMPLOYED BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES WHICH MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED, AND THEN ONLY AFTER INSURING THE IMMEDIATE AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY RESUSCITATIVE EQUIPMENT, AND THE PERSONNEL RESOURCES NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES. (See also ADVERSE REACTIONS, PRECAUTIONS, and OVERDOSAGE.) DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE, AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.
- Mixing or the prior or intercurrent use of any other local anesthetic with MARCAINE cannot be recommended because of insufficient data on the clinical use of such mixtures.
- MARCAINE with epinephrine 1:200,000 contains sodium metabisulfite, a sulfite that may cause allergictype reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people. Single-dose ampuls and single-dose vials of MARCAINE without epinephrine do not contain sodium metabisulfite. For more information on Precautions, please see cited package insert.

Naropin (ropivacaine)(4)

- CONTRAINDICATIONS: Naropin is contraindicated in patients with a known hypersensitivity to ropivacaine or to any local anesthetic agent of the amide type.
- Local anesthetics should only be administered by clinicians who are well versed in the diagnosis and management of doserelated toxicity and other acute emergencies which might arise from the block to be employed, and then only after insuring the immediate (without delay) availability of oxygen, other resuscitative drugs, cardiopulmonary resuscitative equipment, and the personnel resources needed for proper

management of toxic reactions and related emergencies (see also ADVERSE REACTIONS, PRECAUTIONS and MANAGEMENT OF LOCAL ANESTHETIC EMERGENCIES). Delay in proper Reference ID: 4344175 9 management of dose-related toxicity, underventilation from any cause, and/or altered sensitivity may lead to the development of acidosis, cardiac arrest and, possibly, death.

- Naropin should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics, since the toxic effects of these drugs are additive.
- Patients treated with class III antiarrhythmic drugs (e.g., amiodarone) should be under close surveillance and ECG monitoring considered, since cardiac effects may be additive.
- Methemoglobinemia Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6- phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing Reference ID: 4344175 10 clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. Signs of methemoglobinemia may occur immediately or may be delayed some hours after exposure, and are characterized by a cyanotic skin discoloration and/or abnormal coloration of the blood. Methemoglobin levels may continue to rise; therefore, immediate treatment is required to avert more serious central nervous system and cardiovascular adverse effects, including seizures, coma, arrhythmias, and death. Discontinue Naropin and any other oxidizing agents. Depending on the severity of the signs and symptoms, patients may respond to supportive care, i.e., oxygen therapy, hydration. A more severe clinical presentation may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen. For more information on Precautions, please see cited package insert.

2.4.2 Known Potential Benefits

There is no benefit to the individual participant. The results of this study will help inform choice of local anesthetics in dermatologic surgery.

2.4.3 Assessment of Potential Risks and Benefits

The maximum safe doses of commonly used anesthetics are known. Allergies to local anesthetic are also exceedingly rare, with allergic reactions to lidocaine representing only 1% of all adverse reactions.(13) The suggested maximum single infiltration dose of Lidocaine + epinephrine is 6-7 mg/kg, bupivacaine is 2.5-3 mg/kg, and ropivacaine is 3-4 mg/kg.(2) For example, a 58kg (~130 lb) individual may not exceed a single dose of 40.6 mL of lidocaine, or 34.8 mL of bupivacaine, or 116 mL of ropivacaine at a time. We plan to use a minimal effective

dose of 0.5mL of each anesthetic per site, in addition to local anesthesia required for the Mohs surgery. We do not anticipate any side effects or anesthetic toxicity. As such, the study poses minimal risk to the patients.

No agents in this study will be mixed, though their use will be concurrent at separate sites. The simultaneous use of short and long-acting local anesthetics is considered safe and is common in Mohs surgery, having been studied extensively.(5)

Risk of the additive effects of Ropivacaine with Class III anti-arrhythmics is mitigated given the small doses used in this study as systemic absorption of these local anesthetics will be minimal. Though there is a small risk of induced methemoglobinemia with local anesthetics, this risk will be mitigated as patients will be monitored for the duration of the study (3-4 hours) and instructed to seek immediate medical attention if they become symptomatic.

There may be a small risk of ecchymosis at the injection site, however we will use a small quantity of injection and a 30-gauge needle to minimize this risk. The risk of infection will be minimal due to appropriate skin preparation with antiseptic. We do not anticipate any adverse reactions in this study. The knowledge gained from this study which aims to improve patient comfort, anxiety and thus risk of bleeding and other associated risks, and reduce the overall amount of local anesthetic given by potentially revealing the futility in additional injections. This far outweighs the minimal risk associated with additional doses of commonly used local anesthetics utilized as standard of care. To this end, we've completed a similar study utilizing the same amount of a single anesthetic in >50 participants without a single adverse event, including minimal risks such as ecchymosis at the site of injection.

2.5 Correlative Studies Background

Not applicable.

3. Study Design

3.1 Overall Design

For this proposed observational study, we will compare the duration of local anesthetics (Lidocaine + epinephrine, ropivacaine and bupivacaine)at a highly vascularized region of the skin, the nasal ala.

Subject recruitment: Volunteers will be recruited from the general population as well as current patients undergoing MMS. Given that MMS often takes multiple hours, interested patients will be eligible to participate in the study during their MMS day as long as relevant injection sites are not involved in their surgery.

Intervention: After receiving written informed consent from each subject, each site of the nasal ala will be tested for normal sensation using sterile 30-gauge needles. Other eligibility criteria will be confirmed. Once determined to be eligible, participants will be randomized to one of the following 3 groups comparing local anesthetics: 1) lidocaine + epinephrine vs. ropivacaine, 2) lidocaine + epinephrine vs. bupivacaine, 3) ropivacaine vs. bupivacaine. Participants in the trial who are recruited after these three initial groups

have been fully enrolled will join a fourth cohort. Participants in this fourth cohort will receive two different volumes of the same local anesthetic (0.5 ml and 1.0 ml lidocaine with epinephrine).

Data from this fourth cohort, which will compare two doses of the same anesthetic, will be analyzed separately from the data collected from cohorts 1-3.

Laterality of each anesthetic (or volume of anesthetic) administration will also be randomly assigned for each patient. Previous studies have utilized alcohol-sterilized safety pins to test for sensation, however, using sterile needles will be more clinically relevant to dermatologic surgery[14]. Furthermore, using a sterile needle will remove any risk of infection compared to using a safety pin. The injection sites will be cleansed with an isopropyl alcohol swab, and allowed to dry. 0.5mL of local anesthetic will be injected into the skin of each participant by the one dermatologic surgeon (PI of the study, Dr. Kira Minkis, KM). Dr. Minkis will be unblinded to the laterality of the anesthetics and will not be involved in further assessments.

Sites: In order to compare the duration of different anesthetics, we will utilize a split-face design (figure 2).

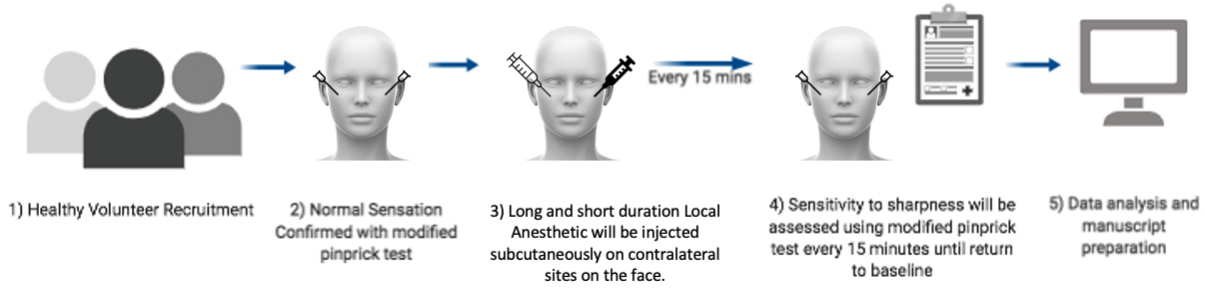


Figure 2: Schematic of the proposed split-face study design comparing long-acting to short-acting anesthetic at the face.

Randomization, blinding and anesthetic choice: For this study, there will be two different investigators taking part in the intervention and assessment. KM will inject the local anesthetic in each patient, while the co-investigator will assess for sensation and administer surveys. The anesthetics of interest include lidocaine + epinephrine, ropivacaine, and bupivacaine. For each of the first three cohorts, 2 of 3 anesthetics will be utilized and the duration compared to one another at a single site. For the fourth cohort, two volumes of a single local anesthetic will be used (0.5 ml and 1.0 ml lidocaine with epinephrine). As each anesthetic is injected to the mirror opposite side at each site, the side at which a single anesthetic will be injected will be randomized as follows: Each of the 2 anesthetics for a single cohort will be numbered 1 or 2. A randomized list of will be generated for each subject of the cohort as outlined in table 1 to determine which anesthetic (1 or 2) will be injected to which side of the chosen anatomic site (Left or Right). For each subject, a card will be created and held within a folder within the clinic space to guide KM in which anesthetic will be injected into which side. KM will not be blinded to the anesthetic choice and corresponding side, but the co-investigator

assessing for sensation will not have access to the list or card until study end, at which the data sheet will be corrected with the anesthetic choice for each side, thus blinding the co-investigator and participant to anesthetic choice during the study.

Table 1. An example of a randomized list of anesthetic choice and side of site association.

Subject ID	Right	Left
1	*1*	*2*
2	*2*	*1*
3	*1*	*2*

Cohorts: Each cohort has been outlined below..

Table 2. Outline of cohorts.

Cohort	Sample size (n)	Site	Route	Anesthetic A	Anesthetic B
1	25	Nasal ala	Subcutaneous local injection	Lidocaine + epinephrine	Ropivacaine
2	25	Nasal ala	Subcutaneous local injection	Lidocaine + epinephrine	Bupivacaine
3	25	Nasal ala	Subcutaneous local injection	Ropivacaine	Bupivacaine
4	25	Nasal ala	Subcutaneous local injection	0.5 ml Lidocaine+ epinephrine	1.0 ml Lidocaine+ epinephrine

Assessment of anesthesia: Subjects will be evaluated for duration of effect of anesthesia every 15 minutes on both sides of the face, until the patient reports return of a sharp sensation upon the pinprick test. The tester and the participants will be blinded to the laterality of the anesthetic. The return of the sensitivity will be measured by binary outcomes (yes/no) using a standardized template (see supporting documentation). The proposed local anesthetics have a quick onset (60 second-5 minutes), and a duration time of 60-400 mins. Thus, we will begin conducting the modified pinprick test prior to the injection (baseline response), immediately following injection, and at 15-minute intervals until return to baseline.

3.2 Scientific Rationale for Study Design

Perioperative anxiety, which can lead to elevated blood pressure and syncope, is a risk factor for intraoperative and postoperative bleeding. By delineating the duration of anesthesia by anatomical regions, we can intervene and provide additional anesthesia earlier before the patients experience pain. This will ensure patients will have maximal comfort and decreased anxiety throughout their surgical procedure by appropriately re-anesthetizing areas in a site-specific manner, or using longer acting anesthetics. Characterizing and defining the duration of local anesthesia will allow clinicians to better

utilize the appropriate frequency of injection of lidocaine in different anatomical sites. A better knowledge of the duration of action of local anesthetic would ensure patient comfort when operating at specific anatomical regions.

3.3 Justification for Dose

We plan to use a minimal effective dose of 0.5mL of 1% lidocaine with epinephrine 1:100,00, a common dose for local anesthesia as required for Mohs surgery. We will also use a dose 1.0 mL of 0.5% lidocaine with epinephrine in order to measure the difference that the volume of anesthetic used makes in a highly vascular area.

We plan to use a minimal effective dose of 0.5mL of 0.5% Marcaine (bupivacaine), a common dose for local anesthesia as required for Mohs surgery.

We plan to use a minimal effective dose of 0.5mL of 0.5% ropivacaine, a common dose for local anesthesia as required for Mohs surgery.

3.4 End of Study Definition

Single visit study

4. Subject Selection

4.1 Study Population

Volunteers who meet the inclusion and exclusion criteria will be eligible for participation in this study. Current patients undergoing MMS will be eligible to participate in the study.

4.2 Inclusion Criteria

1. Male or female ≥ 18 years of age
2. Normal skin sensation at both nasal ala assessed by pinprick
3. Ability to provide informed consent

4.3 Exclusion Criteria

1. Previous adverse reaction to local anesthetic or any components of the local anesthetics being evaluated
2. Pregnant or breastfeeding volunteers (assessed by self-report)
3. Patients taking monoamineoxidase inhibitors (MAOI) or antidepressants of the triptyline or imipramine types

4.4 Lifestyle Considerations

Not applicable

4.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) will not be rescreened.

4.6 Strategies for Recruitment and Retention

•Anticipated accrual rate will be 50%. The target sample size will include both women and men, regardless of the race and ethnicity.

•We will recruit at 1 site only (Department of Dermatology, Weill Cornell Medicine) and we anticipate a total of 75 patients will be recruited. Each patient will be randomized to one of 3 cohorts in which the following local anesthetics will be compared: 1) Lidocaine + epinephrine vs. Ropivacaine, 2) Lidocaine + epinephrine vs. Bupivacaine, 3) Ropivacaine vs. Bupivacaine. There will be 25 patients in each cohort following randomization.

•Print advertisement (local recruitment flyers), online advertisement and word of mouth will be used to recruit participants.

•The source of participants will be the general public, previous and current MMS patients who will agree to participate in the study.

•Potential participants will be approached by the study PI and research assistants. The research team will explain the purpose of the study, and convey that the participation is voluntary and will not influence future treatments directly.

•Patients will be consented in the clinic after recruitment and screening. They will be provided with a copy of the consent to review and take with them.

•Vulnerable participants, such as those who lack consent capacity, including the mentally ill, prisoners, cognitively impaired participants, children, will not be recruited or enrolled in the study.

5. Registration Procedures

5.1 Subject Registration (WCM only)

Subjects will be registered within the WRG-CT as per the standard operating procedure for Subject Registration.

5.2 Subject Registration (Sub-sites)

Not applicable

6. Study Procedures

6.1 Schedule of Assessments

Table 3. Schedule of trial events

	Visit 1
Informed consent	X
Demographics	X
Medical history	X
Concurrent meds	X
Vital signs	X
Height	X
Weight	X
Baseline pinprick evaluation	X
Confirm eligibility/randomization	
Study product administration	X
Adverse event evaluation	X
Outcome evaluation: Pinprick test	X

during the procedure	

7. Study Intervention

7.1 Study Intervention/Device Description

The agents utilized in the study intervention include 3 local anesthetics. Xylocaine + epinephrine 1:100,000 (lidocaine + epinephrine 1:100,000), buffered 1/10 with sodium bicarb, Marcaine (bupivacaine) 0.5% and Naropin (ropivacaine) 0.5%. All anesthetics will be drawn up using 18-gauge syringe needles into 1cc syringes. All injections will be done with 30-gauge needs.

7.2 Availability

The agents used in this study are available in the PI's dermatology practice, supplied by WCM Department of Dermatology.

7.3 Acquisition and Accountability

Agent Inventory Records/Device Logs – The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory of study medications and adhere to relevant policies regarding storage of medications.

7.4 Formulation, Appearance, Packaging, and Labeling

This study will utilize existing supply channels to obtain drug. These are generally multiuse vials. The specific brand and manufacturer may vary over the course of the study.

7.5 Product Storage and Stability

All agents should be stored at room temperature, approximately 25C (77F) and protected from light.

7.6 Preparation

0.5 mL in syringes of each anesthetic will be prepared by practice staff. Xylocaine + epinephrine 1:100,000 (lidocaine + epinephrine 1:100,000) is buffered with sodium bicarbonate (1/10). Otherwise 0.5 mL of each anesthetic will be drawn directly from manufacturing bottle. All anesthetics will be drawn up using 18-gauge syringe needles

into 1cc syringes. All injections will be done with 30-gauge needs.

7.7 Dosing and Administration

7.7.1 Dosing Delays/Dose Modifications

NA

7.8 General Concomitant Medication and Supportive Care Guidelines

NA

7.9 Duration of Therapy and Criteria for Removal from Study

In this section, please describe the duration of study therapy and reasons for discontinuation from therapy.

Example text provided as a guide, customize as needed:

This study will require a single visit. The study termination guidelines are as follows:

Subject's voluntary withdrawal

- Return to normal sensation of both sides

7.10 Duration of Follow Up

NA

7.11 Measures to Minimize Bias: Randomization and Blinding

For this study, there will be two different investigators taking part in the intervention and assessment. KM will inject the local anesthetic in each patient, while the co-investigator will assess for sensation and administer surveys. The anesthetics of interest include lidocaine + epinephrine, ropivacaine, and bupivacaine. For each cohort, 2 of 3 anesthetics will be utilized and the duration compared to one another at a single site. As each anesthetic is injected to the mirror opposite side at each site, the side at which a single anesthetic will be injected will be randomized as follows: Each of the 2 anesthetics for a single cohort will be numbered 1 or 2. A randomized list of will be generated for each subject of the cohort as outlined in table 1 to determine which anesthetic (1 or 2) will be injected to which side of the chosen anatomic site (Left or Right). For each subject, a card will be created and held within a folder within the clinic space to guide KM in which anesthetic will be injected into which side. KM will not be blinded to the anesthetic choice and corresponding side, but the co-investigator assessing for sensation will not have access to the list or card until study end, at which the data sheet will be corrected with the anesthetic choice for each side, thus blinding the co-investigator and participant to anesthetic choice during the study.

Each patient will be randomized to one of 3 cohorts in which the following local anesthetics will be compared: 1) Lidocaine + epinephrine vs. Ropivacaine, 2) Lidocaine + epinephrine vs. Bupivacaine, 3) Ropivacaine vs. Bupivacaine. There will be 25 patients in each cohort following randomization. See table 2.

7.12 Study Intervention/Follow-up Compliance

Not applicable.

8. Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

8.1 Discontinuation of Study Intervention

Each participant will receive 2 injections as the intervention, which will take place during a single visit without further intervention. If the participant discontinues from the study intervention, such as refusing the second injection, they will not be included in the study as the primary endpoint will not be obtainable/measurable.

8.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Participant unable to receive the second injection or refuses the second injection

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

8.3 Lost to Follow Up

Not applicable.

9. Correlative/Special Studies

Not applicable

10. Measurement of Effect

10.1 Response Criteria

The primary aim of this study is to determine whether the time to return to baseline sensation (in minutes) differs significantly between each pair of anesthetics. Since each

patient will receive two anesthetics, we will calculate the difference in anesthetic durations measured by pin-prick test in minutes for each patient and perform a paired t-test within each cohort to assess whether time to return to baseline sensation significantly differed.

10.2 Duration of Response

Not applicable.

10.3 Progression-Free Survival

Not applicable.

10.4 Other Response Parameters

None

11. Data Reporting / Regulatory Considerations

11.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, efficacy, and adverse event data for all enrolled subjects.

11.1.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

11.2 Regulatory Considerations

11.2.1 Institutional Review Board/Ethics Committee Approval

As required by local regulations, the Investigator will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, before study initiation.

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate Ethics Committee. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the IP is released to the Investigator. Any necessary extensions or renewals of IRB approval must be obtained for changes to the study, such as amendments to the protocol, the ICF,

or other study documentation. The written approval of the IRB together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IRB any new information that may adversely affect the safety of the patients or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB as required. On completion of the study, the IRB will be notified that the study has ended.

All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

Once protocol amendments or consent form modifications are implemented at the lead site, Weill Cornell Medicine, updated documents will be provided to participating sites, as applicable. Weill Cornell Medicine must approve all consent form changes prior to local IRB submission.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

11.2.2 Ethical Conduct of the Study

The Investigators and all parties involved should conduct this study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines and the applicable national and local laws and regulatory requirements.

This study will be conducted under a protocol reviewed and approved by the applicable ethics committees and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

11.2.3 Informed Consent

The investigator or qualified designee must obtain documented consent according to ICH-GCP and local regulations, as applicable, from each potential subject or each subject's legally authorized representative prior to participating in the research study. Subjects who agree to participate will sign the approved informed consent form and will be provided a copy of the signed document.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must approved by IRB prior to use. The ICF will adhere to IRB requirements, applicable laws and regulations.Consent will not be remote or electronic, but instead by signature on paper record kept on file in a secure location within the PI's office.

11.2.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor-Investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

11.2.5 Record Retention

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the IP. In addition, all subjects medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

12. Statistical Considerations

12.1 Study Design/Endpoints

Eligible participants will be randomized into one of three cohorts and receive two different local anesthetics (Lidocaine + epinephrine vs Ropivacaine, Lidocaine + epinephrine vs Bupivacaine or Ropivacaine vs Bupivacaine) administered to both [sides of the nose]. We will assay the duration of local anesthetic at 15-minute increments using a modification of the previously published non-invasive pinprick testing. The co-investigator and participant will be blinded to the side (left or right) to which each anesthetic is injected. The primary endpoint will be the time to return to baseline sensation (in minutes), as measured by a modification of the previously published non-invasive pin-prick testing method, and recorded by the questionnaire.

12.2 Sample Size/Accrual Rate

We anticipate recruiting 75 participants for this study. This sample size is based on patient census and other logistical factors. We will randomize each patient to one of three anesthetic comparison cohorts (as shown in Table 2), resulting in 25 patients per cohort. Within each cohort, the laterality of each anesthetic will also be randomized for each patient. We will aim to recruit all participants by 5 months. In previous work, we've recruited a cohort of 25 participants in 4-5 weeks.

12.3 Stratification Factors

Not applicable.

12.4 Analysis of Endpoints

12.4.1 Analysis of Primary Endpoints

The primary aim of this study is to determine whether the time to return to baseline sensation (in minutes) differs significantly between each pair of anesthetics. Since each patient will receive two anesthetics, we will calculate the difference in anesthetic durations for each patient and perform a paired t-test within each cohort to assess whether time to return to baseline sensation significantly differed. Our hypothesis is that none of the cohorts will show a significant difference in duration between anesthetics.

The maximum difference in anesthetic duration that we consider “not different” from a clinical standpoint is 15 minutes. Using this as an estimate of the mean of paired differences in a paired t-test with a sample size of N=25 and 5% alpha level, we can expect 82% power or greater if the standard deviation of the paired differences is 25 minutes or less. We will consider the treatments not different if the 95% confidence interval for the absolute difference is contained within (-15 minutes to +15 minutes). We will not adjust for multiple comparisons.

12.4.2 Analysis of Secondary Endpoints

The secondary aim of this study is to examine which patient characteristics are associated with the duration of each local anesthetic. We will use Pearson’s correlation coefficient, or a non-parametric equivalent, to examine the association between patient characteristics measured on a continuous scale (e.g., age, BMI, etc.) and anesthetic duration, and we will perform independent samples t-tests, ANOVAs, or their non-parametric equivalents, to examine the association between categorical patient characteristics (e.g., gender, hair color, etc.).

Descriptive statistics (mean/SD for continuous variables and frequency/percent for categorical variables) will be calculated for all patient characteristics, and for anesthetic durations and paired differences in each cohort. All tests will be two-sided, assuming a 5% alpha level, and 95% confidence intervals will be computed, where appropriate, to show the precision of the obtained estimates. All analyses will be performed in SAS Version 9.4 (SAS Institute, Inc., Cary, NC)

Note: The statistical considerations section was written in conjunction with Debra D’Angelo, MS, in the Division of Biostatistics, Department of Population Health Sciences at Weill Cornell Medicine.

12.5 Interim Analysis

Not Applicable. All analysis will be conducted at the completion of the study.

12.6 Reporting and Exclusions

12.6.1 Evaluation of Toxicity

All subjects will be evaluable for toxicity from the time of their first treatment with the local anesthetics.

12.6.2 Evaluation of Response

All subjects included in the study will be assessed for response to treatment if they have received both injections of local anesthetic.

13. Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by subjects or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

13.1 Adverse Event Definition

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

13.1.1 Investigational Agent or Device Risks (Expected Adverse Events)

We do not anticipate any side effects or anesthetic toxicity. As such, the study poses minimal risk to the patients. Subjects will experience pain with the injection. There may be a small risk of ecchymosis at the injection site, however we will use a small quantity of injection and a 30-gauge needle to minimize this risk. The risk of infection will be minimal due to appropriate skin preparation with antiseptic. We do not anticipate any adverse reactions in this study.

13.1.2 Adverse Event Characteristics and Related Attributions

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.

- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

13.1.3 Recording of Adverse Events

All adverse events grade 3 or greater and any serious adverse events will be recorded on a subject specific AE log. The AE log will be maintained by the research staff and kept in the subject's research chart.

13.1.4 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.1.5 Reporting Events to Participants

NA

13.1.6 Events of Special Interest

Not applicable.

13.1.7 Reporting of Pregnancy

Not applicable.

13.2 Definition of SAE

SAEs include death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

13.2.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.2.2 Reporting of SAE to FDA [For Protocols Where WCMC is the Sponsor-Investigator]

IND application sponsor must report any suspected adverse reaction or adverse reaction to study treatment that is both serious and unexpected. Unexpected fatal or life-threatening suspected adverse reactions represent especially important

safety information and must be reported to FDA as soon as possible but no later than 7 calendar days following the sponsor's initial receipt of the information.

i. death,
ii. a life-threatening adverse event,
iii. in-patient hospitalization or prolongation of existing hospitalization,
iv. a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
v. a congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or research subject and may require medical or surgical intervention to prevent one of the outcomes listed as serious

13.3 AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the subject discontinues participation from the study.

13.4 Time Period and Frequency for Event Assessment and Follow Up

AEs will be assessed through the end of study participation in this one visit study.

14. Unanticipated Problems Involving Risks to Subjects or Others

14.1 Definition of Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

14.1.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPIRTSOs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UPIRTSO report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UPIRTSO;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UPIRTSO.

To satisfy the requirement for prompt reporting, UPIRTSOs will be reported using the following timeline:

- UPIRTSOs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the event.
- Any other UPIRTSO will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), Food and Drug Administration (FDA), and the Office for Human Research Protections (OHRP) within <insert timeline in accordance with policy> of the IRB's receipt of the report of the problem from the investigator.]

15. Data and Safety Monitoring Plan (DSMP)

This study will be monitored by the study team only. The agents being study are being used on label and pose minimal risk to the participant. If a single Grade 4 or SAE occurs, the study will halt until an external advisory group can be convened and the IRB has reviewed the event.

Data and events that will be captured and submitted:

All Grade 3 or greater AEs and SAEs will be recorded. This includes but is not limited to local and systemic reactions to both tissue trauma (needle injection) and/or the agent used. The capturing template is outlined in table 5.

Table: Monitoring entity reporting and review

Data type	Frequency of review	Reviewer
Subject accrual (including compliance with protocol enrollment criteria)	Quarterly	PI, study team
Status of all enrolled subjects, as of date of reporting	Quarterly	PI, study team

Data type	Frequency of review	Reviewer
Adherence data regarding study visits and intervention	Quarterly	PI, study team
AEs	Quarterly	PI, study team
SAEs	Per occurrence	PI, study team, external advisory group

Study stopping rules:

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial

Protection of subject privacy:

During this study, all of the data collected are for research purposes only and data will be kept in strict confidence. No information will be given to anyone without permission from the participant. The consent form includes the informed consent statement required by the IRB and Weill Cornell Medicine for interventional studies. This statement guarantees confidentiality and identifies the participant as the owner of the data gathered. Confidentiality will be ensured by use of deidentification. All data, whether generated in the laboratory or at the bedside, will be identified with a randomly generated identification code unique to the participant.

The only risk of this study is a breach of confidentiality, which will be avoided by the following methods. No published data will be associated with participant names, or other elements of PHI. Unique study identifiers will be used in place of participant names and medical record numbers. All deidentified data will be saved electronically on a password protected computer that has been tagged by WCM. Only the PI and study personnel will have access to this data. After completion of this research, all data will be deleted.

Database protection:

The database will be secured with password protection. The informatics manager will receive only coded information that is entered into the database under those identification numbers. Electronic communication with outside collaborators will involve only unidentifiable information.

Confidentiality during Adverse Event (AE) Reporting:

AE reports and annual summaries will not include subject-identifiable data. Each report will only include the participant identification code.

16. References

Please provide the citations for all publications referenced in the text.

1. Administration FaD. Xylocaine (lidocaine HCl and epinephrine Injection, USP) 2010 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/006488s074lbl.pdf.
2. Iowa Uo. Maximum Recommended Doses and Duration of Local Anesthetics [updated October 13, 2019. Available from: https://medicine.uiowa.edu/iowaprotocols/maximum-recommended-doses-and-duration-local-anesthetics.
3. Administration FaD. Marcaine. 2011.
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5. Chen P, Smith H, Vinciullo C. Bupivacaine as an Adjunct to Lidocaine in Mohs Micrographic Surgery: A Prospective Randomized Controlled Trial. Dermatol Surg. 2018;44(5):607-10.
6. Sorenson E, Chesnut C. Liposomal Bupivacaine: A Review and Applications to Dermatologic Surgery. Dermatol Surg. 2019;45(1):68-73.
7. Yadlapati S, Kaul S, Jakhar D. Liposomal bupivacaine infiltration as an effective option for postoperative pain management after Mohs surgery. Int J Dermatol. 2021.
8. Drugs.com Drugs.com [Available from: https://www.drugs.com/.
9. Collins JB, Song J, Mahabir RC. Onset and duration of intradermal mixtures of bupivacaine and lidocaine with epinephrine. Can J Plast Surg. 2013;21.
10. Boen M, Alhaddad M, Goldman MP, Kollipara R, Hoss E, Wu DC. A Randomized, Evaluator-Blind, Split-Face Study Evaluating the Safety and Efficacy of Calcium Hydroxylapatite for Jawline Augmentation. Dermatol Surg. 2022;48(1):76-81.
11. Weiss R, Bank D, Brandt F. Randomized, Double-Blind, Split-Face Study of Small-Gel-Particle Hyaluronic Acid with and without Lidocaine During Correction of Nasolabial Folds. Dermatol Surg. 2010;36(1):750-9.
12. Alexanian CC, Zhuang AR, Crispin MK, Armstrong AW, Eisen DB. Wound eversion versus planar closure for wounds on the face or neck: A randomized split-wound comparative effectiveness trial. J Am Acad Dermatol. 2020;83(5):1439-40.
13. Kouba DJ, LoPiccolo MC, Alam M, Bordeaux JS, Cohen B, Hanke CW, et al. Guidelines for the use of local anesthesia in office-based dermatologic surgery. J Am Acad Dermatol. 2016;74(6):1201-19.