Kinetic Anesthesia Device for Lidocaine Injection: a randomized split-body study of the effects of kinetic anesthesia devices on pain of lidocaine injection in healthy volunteers.

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NIH Grant Number	Include NIH grant number if applicable
Investigational Product:	Blaine Labs Vibration Anesthesia Device
IRB Number:	828686

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Study Summary

Title	**Kinetic Anesthesia Device for Lidocaine Injection: a randomized split-body study of the effects of kinetic anesthesia devices on pain of lidocaine injection in healthy volunteers.**
Short Title	**Kinetic Anesthesia Device Study**
IRB Number	Pending
Protocol Number	Pending
Phase	Not applicable
Methodology	open label split-body crossover trial with randomization of subjects to one of three injection locations, and randomization of the order of injection with and without intervention.
Study Duration	Recruitment and enrollment period: 2 months Subjects' length of participation in the study: 1 visit. The entire encounter should take less than one hour. Project date of the proposed study: Recruitment and enrollment will commence with IRB approval. Total duration: 6 months in total for full data processing.
Study Center(s)	Single center – the study will take place at the Perelman Center For Advanced Medicine.
Objectives	Primary: To determine the effect of kinetic devices versus no device on pain of lidocaine injection as measured by 100mm visual analog scale. Secondary: To determine if the effect of kinetic devices on pain of local anesthetic injection is associated with anatomic location of the injection To determine patient preference of kinetic device versus no device for local anesthetic injection To gather qualitative data on changes to the patients experience of pain and overall experience using the kinetic anesthesia device versus no device
Number of Subjects	50

Main Inclusion and Exclusion Criteria	**Key inclusion criteria** 1. Adult volunteers greater than or equal to 18 years of age 2. Able and willing to provide informed consent 3. Able to comprehend and comply with study instructions, and able to complete necessary evaluations. **Key exclusion criteria** 1. Patients unable or unwilling to provide informed consent. 2. Patients with lidocaine allergy 3. Patients with known pain-related or neurological condition. 4.Patients with a known cardiac condition 5. Patients taking medications with a known Clinically Significant Drug Interaction with 6. Vulnerable populations
Investigational Product (drug, biologic, device, etc.) **For Device include the planned use**	Blaine Labs Vibration Anesthesia Device. The device will be used as directed by the manufacturer, in the following manner: The device will be held by the person giving the injection in their off hand. It will be firmly pressed on the skin, turned on, adjacent to the injection 1-2 seconds before the injection is given. The injection will be given into the lighted target area of the kinetic anesthesia device. The device will be removed 1-2 seconds after the needle is withdrawn
For Drug, food, cosmetic, etc. include the dose, route of administration and dose regiment	This device is on the US market legally. This is a class 1 device, exempt from the need for approval or clearance. Per the Code of Federal Regulations (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRsearch.cfm?FR=890.5975-) this device may be used in clinical care or research. The device is being used in this research study in accordance with the FDA description
Statistical Methodology	Quantitative VAS data will be analyzed by a two-tailed t-test, and by linear regression model, incorporating location, and order of intervention (i.e. intervention first or second). Quantitative preferential data will be analyzed by logistic regression model incorporating location and order of intervention.
Safety Evaluations	Patients will be monitored for physical discomfort following lidocaine injection by experienced healthcare personnel. Any health-related events will be handled in accordance with standard of care clinical procedures.
Data and Safety Monitoring Plan	The Principal investigator will be responsible for monitoring the data quality and the ongoing safety of subjects.

BACKGROUND AND STUDY RATIONALE

This study will be conducted in full accordance all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations including [as applicable include the following regulations as they apply 45 CFR 46, 21 CFR Parts 50, 54, 56, 312, 314 and 812 and Good Clinical Practice: Consolidated Guidelines approved by the International Conference on Harmonisation (ICH). Note:Only include ICH compliance if the study will actually comply with these requirements.] All episodes of noncompliance will be documented.

Introduction

Lidocaine is used widely in the field of dermatology for anesthetizing the skin. It is used commonly for minor procedures such as punch biopsies, and more complex outpatient facial reconstruction after skin cancer removal. Patients consistently experience discomfort from lidocaine injections, particularly since procedures on highly sensitive areas such as the nose and lips are common. Vibrating kinetic anesthesia devices have shown efficacy in reducing the pain of lidocaine injections in dentistry, pediatrics, and dermatology, however no studies exist investigating the effect of these devices on the pain of lidocaine injections on the face.

The proposed study is a split-body randomized controlled trial of kinetic anesthesia devices on pain of lidocaine injection measured by a visual analog scale (VAS). Study participants will be healthy adult volunteers recruited from students, faculty, staff, and others healthy adult within the University of Pennsylvania. The study intervention will be application of the Blaine Labs Vibration Anesthesia Device at the time of injection, according to the manufacturer's instructions. Participants will rate the pain from one injection with the kinetic anesthesia device (KAD) in use, and one injection without the KAD. Ratings will occur on a VAS. Participants will be asked whether they preferred the injection with or without the KAD. Injections will occur at these three sites: lateral forehead, nasofacial sulcus, and lateral back. Participants will be randomized to one of three locations, and to the order of intervention (i.e. first or second injection with KAD). Injections with and without the intervention will occur on the right and left side of the body respectively.

1.1 Background and Relevant Literature

In many dermatologic procedures performed with local anesthetic, the injection of anesthetic is the most painful part of the procedure, and is thus one of the greatest barriers to complete comfort and enhanced patient satisfaction. Methods to minimize injection pain have been proposed and include slow rate of injection, with warmed, buffered lidocaine to decrease discomfort of local anesthetic injection (Kuboa), Vibrating devices have been shown to reduce the pain of local botulinum toxin injections, steroid injections for keloid treatment , local anesthetic injections in eyelid surgery , and in venipuncture in a pediatric emergency department. It is thought that vibration decreases the pain of injection by the gate control theory of pain, first proposed by Melzack and Wall, which asserts that the vibrating neural input overrides painful signals and prevents them from reaching the central nervous system. No study has yet investigated vibration devices for lidocaine injection at multiple body sites in the dermatologic surgery setting. The VAS is reported to be the most frequently used assessment instrument to evaluate the analgesic effects of various therapies and can detect minute pain changes. It has been systematically evaluated by Bijur et al, who determined that a change of 10mm or more on this scale represents a real clinical change in acute pain.

Kuboa et al. Guidelines for the use of local anesthesia in office-based dermatologic surgery. JAAD. 2016;74:6:1201-1219 Sharma P, et al. Investigating the efficacy of vibration anesthesia to reduce pain from cosmetic botulinum toxin injections. Aesthet Surg J.
2011;31:966-971 Park KY, Kim BJ et al. Vibration Anesthesia for Pain Reduction During Intralesional Steroid Injection for Keloid Treatment. Derm Surg. 2017;43:724-727. Fayers, T et al. Vibration-assisted anesthesia in eyelid surgery. Othalmology. 2010;117:1453-1457 Baxter AL et al. An integration of vibration and cold relieves venipuncture pain in a pediatric emergency department. Pediatr Emerg Care.

2011;27:1151-1156 KC Smith, JC Liu et al. Vibration anesthesia: A noninvasive method of reducing discomfort prior to dermatologic procedures. Dermatology Online Journal. 2004;10(2):1 Reed Michael D, van Nostran W. Assessing pain intensity with the visual analog scale: a plea for unity. J Clinic Pharm. 2014; 54:241-244. Bijur PE, Silver W, Gallagher EJ. Reliabil15.

1.2 Name and Description of the Investigational Product

Blaine Labs Vibration Anesthesia Device. The device will be used as directed by the manufacturer, in the following manner: The device will be held by the person giving the injection in their non-dominant hand. The vibrating device will be firmly pressed on the skin, turned on, adjacent to the injection 1-2 seconds before the injection is given. The injection will be given into the lighted target area of the KAD. The device will be removed 1-2 seconds after the needle is withdrawn

This device is on the US market legally. This is a class 1 device, exempt from the need for approval or clearance. Per the Code of Federal Regulations (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRsearch.cfm?FR=890.5975-) this device may be used in clinical care or research.

The device is being used in this research study in accordance with the FDA description

Further information regarding the device is attached in HS-ERA.

1.2.1 Clinical Data to Date

Clinical data is summarized in the background section above.

2 Study Objectives

Overall objectives
The purpose of this study is to test the effect of KAD on the pain of lidocaine injection in healthy adult volunteers at sites with clinical relevance in dermatologic surgery. Primary Objectives: To determine the effect of KAD versus no device on pain of local anesthetic injection measured by VAS
Secondary Objectives: 1. To determine if the effect of KAD on pain of local anesthetic injection is associated with anatomic location of the injection; 2. To determine subject preference of KAD versus no device for local anesthetic injection; 3. To gather qualitative data on changes to the subjects' experience of pain and overall experience using the KAD versus no device.

2.1 Primary Objective

To determine the effect of KAD versus no device on pain of lidocaine injection, participants will be asked to evaluate each injection on a 100mm visual analog scale (VAS). Ratings will be quantified at intervals of 1mm from 1mm to 100mm, with 1 mm representing "no pain at all" and 100 mm representing "worst pain imaginable." VAS ratings from injections with and without the device will be compared in each patient.

2.2 Secondary Objectives (if applicable)

To determine if the effect of KAD on pain of local anesthetic injection is associated with anatomic location of the injection, VAS ratings will be used within a statistical model. To determine subject preference of kinetic device versus no device for local anesthetic injection, participants will be asked after the completion of their second injection: "Which method of injection did you prefer overall?" with the following answers: "With the vibrating kinetic anesthesia device being used" "without the vibrating kinetic anesthesia device" and "no preference" To gather qualitative data on changes to the subjects' experience of pain and overall experience using KAD versus no device, patients will be asked the following questions: "Do you have any comments on how the KAD affected your

injection experience?" "Were you bothered in any way by the KAD [check yes or no] if so please comment".

3 Investigational Plan

3.1 General Design

The study will be an open label split-body crossover trial, using healthy adult volunteers recruited from the faculty, staff and student body of the University of Pennsylvania, and from the University City area of Philadelphia. Participants will be randomized to one of three anatomic sites deemed relevant: the nasofacial sulcus, the lateral forehead, and the upper back. Participants will then be randomized to receive injection with the KAD first or second. The injection will be 0.5 cc of room temperature buffered lidocaine injected at constant slow speed (approximately 5 seconds) through a 30-gauge needle held perpendicular to the skin by the same surgeon, with verbal cues standardized. Injections will be given in accordance with the standard of practice. When the KAD is used it will be used as directed: firmly pressed on the skin adjacent to the injection, with the needle aimed into the lighted area. Volunteers will evaluate each injection immediately after it is complete using the visual analog scale. When both injections are completed, participants will indicate their preference of injection, complete qualitative questions, and note necessary demographic information. Injection location and order of intervention (i.e. first or second) will be noted.

3.1.1 Screening Phase

Screening will take place at the time of the study. After informed consent and prior to the start of the investigative procedure, subjects will be verbally asked if they have preexisting cardiac conditions, neurological conditions, or previous adverse reactions to lidocaine.

3.1.2 Study Intervention Phase

1. The study will take place in an examination room in the Dermatologic Surgery clinic at the Perelman Center for Advanced Medicine.
2. The KAD used will be the Blaine Labs Vibration Anesthesia Device. The device will be purchased from Blaine Labs directly.
3. Injections will be made up of 0.5mL of room temperature 1% lidocaine buffered with 8.4% sodium bicarbonate, procured from the dermatologic surgery clinic. Injections will use the standard syringe with 30 gauge needle.
4. Before any procedure is done or information is collected for the study, subjects will be asked to read and sign the consent form. Adequate time will be given for subjects to review the Informed Consent Document and review any of their questions or concerns with the study staff or Principal Investigator.
5. Baseline vital signs (heart rate and blood pressure) will be obtained prior to the first injection.
6. Then each subject will be randomized to one location: nasofacial sulcus, lateral forehead or lateral back.
7. Each subject will be randomized to receive the intervention with KAD either first or second.
8. The first injection will always be on the left side and the second will always be on the right
9. When the KAD is used for the injection, it will be held by the person giving the injection in their off hand. It will be firmly pressed on the skin, turned on, adjacent to the injection 1-2 seconds before the injection is given. The injection will be given into the lighted target area of the KAD. The device will be removed 1-2 seconds after the needle is withdrawn.
10. Each injection will be given in accordance with the current standard of practice. Injections will be given using the formulation and needle noted above. Injections will be given with the needle held perpendicular to the skin. The speed of the injection will be slow, aiming for 5 seconds to empty the syringe. All injections will be performed by Dr. Sobanko, with verbal cues standardized.
11. After each injection, study participants will be asked to document their level of acute pain using the VAS. A paper and pen version of the scale will be used.
12. After both injections are complete, safety vitals will again be obtained (heart rate, blood pressure) in order to assess whether subject has tolerated the injection without any adverse reactions. If necessary, repeat vitals will be obtained until the Principal Investigator feels the subject is medically clear to leave.

13. After both injections are complete the study participant will be asked to fill out the short questionnaire about preference of injection, qualitative comments, age, and sex.
14. The location and order of the injections will be noted by study personnel. The VAS scales will be measured.
15. At this point, data collection will be complete. Unless an adverse event was noted, or subject has additional questions or concerns regarding their participation or study-related procedures, participants will be compensated and will be free to go at this point.
16. The kinetic anesthesia device will be cleaned with an alcohol swab. Study personnel will wash hands and repeat the exercise on the next participant.

3.1.3 Allocation to Interventional Group

Participants will be randomized to one of three locations: nasofacial sulcus, lateral forehead, or upper back. Additionally, subjects will be randomized to receive the intervention with vibration anesthesia device on their first (left) or second (right)-sided injection. This is a split body study so each participant will receive 2 total injections – one with and one without the intervention. Randomization will be achieved by the selection of a sealed envelope by each study participant, that will have a location and an order listed. This will randomize subjects and will ensure that groups can be balanced, by creating equal numbers of envelopes for each of the groups.

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

Each injection will be evaluated by 100mm visual analog scale (VAS) for acute pain immediately after the injection is complete. Patients visually indicate by drawing on paper where their pain is on a 10 cm line, with one end labelled no pain at all and the other worst pain imaginable. The primary endpoint is a statistically significant mean reduction in acute pain on VAS of 10mm or more, per Bijur et al, who determined that this change indicates a real clinical change in acute pain.

3.2.2 Secondary Study Endpoints

Following the completion of both injections, volunteers will indicate which injection they preferred, with a no preference option included. Patients will also be queried on demographic information after the injections have been completed. They will be asked age, sex, and role at the University of Pennsylvania. Because pain is characterized as quantitative AND qualitative, there will be a free response section for comments, specifically asking “Do you have any comments on how the kinetic anesthesia device affected your injection experience?” A second qualitative entry section will ask: “Were you bothered in any way by the KAD [check yes or no] if so please comment”

4 Study Population and Duration of Participation

4.1 Inclusion / Exclusion Criteria

Inclusion / Exclusion Criteria will be verified by the Principal Investigator.

4.2 Key inclusion criteria

1. Adult volunteers greater than or equal to 18 years of age
2. Able and willing to provide informed consent
3. Able to comprehend and comply with study instructions, and able to complete necessary evaluations.

4.3 Exclusion Criteria

1. Patients unable or unwilling to provide informed consent.
2. Patients with lidocaine allergy
3. Patients with known pain-related or neurological condition.
4.Patients with a known cardiac condition

5. Patients taking medications with a known Clinically Significant Drug Interaction with lidocaine.
6. Patients who are pregnant or Nursing mothers.
7. Vulnerable populations

4.4 Subject Recruitment

Subject recruitment will occur by email to the Perelman School of Medicine student body. Email text is attached. Further recruitment will occur from flyers posted around the University of Pennsylvania campus and University City area. Flyer attached. Study recruitment information will be circulated via the UPHS broadcast email. Materials attached. The study will be posted on the iConnect tool.

4.5 Duration of Study Participation

Recruitment and enrollment period: 2 months
Subjects' length of participation in the study: 1 day.
The entire encounter should take less than one hour.
Project date of the proposed study: Recruitment and enrollment will commence with IRB approval.
A total time of 6 months is requested for data analysis.

4.6 Total Number of Subjects and Sites

50 subjects enrolled for the study taking place at one site – Perelman Center for Advanced Medicine.

4.7 Vulnerable Populations:

Vulnerable populations will not be included in this study

5 Study Intervention (Study drug, device, biologic, vaccine, food etc.)

5.1 Description

Blaine Labs Vibration Anesthesia Device. The device will be used as directed by the manufacturer, in the following manner: The device will be held by the person giving the injection in their off hand. It will be firmly pressed on the skin, turned on, adjacent to the injection 1-2 seconds before the injection is given. The injection will be given into the lighted target area of the kinetic anesthesia device. The device will be removed 1-2 seconds after the needle is withdrawn.

This device is on the US market legally. This is a class 1 device, exempt from the need for approval or clearance. Per the Code of Federal Regulations (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRsearch.cfm?FR=890.5975-) this device may be used in clinical care or research.

The device is being used in this research study in accordance with the FDA description

Further information regarding the device is attached in HS-ERA.

5.2 Receipt

The device will be purchased directly from Blaine Labs and shipped to Dr. Joseph Sobanko in the Perelman Center for Advanced Medicine.

6 Study Procedures

6.1 Study Intervention Phase

1. The study will take place in an examination room in the Dermatologic Surgery clinic at the Perelman Center for Advanced Medicine.
2. The KAD used will be the Blaine Labs Vibration Anesthesia Device. The device will be purchased from Blaine Labs directly.
3. Injections will be made up of 0.5mL of room temperature 1% lidocaine buffered with 8.4% sodium bicarbonate, procured from the dermatologic surgery clinic. Injections will use the standard syringe with 30-gauge needle.
4. Before any procedure is done or information is collected for the study, subjects will be asked to read and sign the consent form. Adequate time will be given for subjects to review the Informed Consent Document and review any of their questions or concerns with the study staff or Principal Investigator.
5. Baseline vital signs (heart rate, blood pressure,) will be obtained prior to the first injection. The participant's baseline respiratory rate and adequacy of ventilation will also be noted. We will additionally specify that the study procedure will take place in a setting where resuscitative equipment and personnel for treating adverse reactions will be immediately available."
6. Then each subject will be randomized to one location: nasofacial sulcus, lateral forehead or lateral back.
7. Each subject will be randomized to receive the intervention with KAD either first or second.
8. The first injection will always be on the left side and the second will always be on the right
9. When the KAD is used for the injection, it will be held by the person giving the injection in their off hand. It will be firmly pressed on the skin, turned on, adjacent to the injection 1-2 seconds before the injection is given. The injection will be given into the lighted target area of the KAD. The device will be removed 1-2 seconds after the needle is withdrawn.
10. Each injection will be given in accordance with the current standard of practice. Injections will be given using the formulation and needle noted above. Injections will be given with the needle held perpendicular to the skin. The speed of the injection will be slow, aiming for 5 seconds to empty the syringe. All injections will be performed by Dr. Sobanko, with verbal cues standardized.
11. After each injection, study participants will be asked to document their level of acute pain using the VAS. A paper and pen version of the scale will be used.
12. After both injections are complete, safety vitals will again be obtained (heart rate, blood pressure, respiratory rate and adequacy of ventilation) in order to assess whether subject has tolerated the injection without any adverse reactions. If necessary, repeat vitals will be obtained until the Principal Investigator feels the subject is medically clear to leave.
13. After both injections are complete the study participant will be asked to fill out the short questionnaire about preference of injection, qualitative comments, age, and sex.
14. The location and order of the injections will be noted by study personnel. The VAS scales will be measured.
15. At this point, data collection will be complete. Unless an adverse event was noted, or subject has additional questions or concerns regarding their participation or study-related procedures, participants will be compensated and will be free to go at this point.
16. The kinetic anesthesia device will be cleaned with an alcohol swab. Study personnel will wash hands and repeat the exercise on the next participant.

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6.2 Subject Withdrawal

Subjects may withdraw at any time by indicating this to investigators.

7 Study Evaluations and Measurements

Each injection will be evaluated by 100mm visual analog scale (VAS) for acute pain immediately after the injection is complete. Patients visually indicate by drawing on paper where their pain is on a 10 cm line, with one end labelled no pain at all and the other worst pain imaginable. The primary endpoint is a statistically significant mean reduction in acute pain on VAS of 10mm or more, per Bijur et al, who determined that this change indicates a real clinical change in acute pain. Following the completion of both injections, volunteers will indicate which injection they preferred, with a no preference option included. Patients will also be queried on demographic information after the injections have been

completed. They will be asked age, sex, role at University of Pennsylvania. Because pain is characterized as quantitative AND qualitative, include a free response section for comments, specifically asking Do you have any comments on how the kinetic anesthesia device affected your injection experience? A second qualitative entry section will ask: Were you bothered in any way by the VAD [check yes or no] if so please comment

7.1 Vital Signs

Vital signs will be collected by the study staff overseeing the visit. Baseline vitals will be established prior to the first injection and recorded on the data source sheet. Post-Injection Vitals will be obtained following the second injection, before subjects begin to fill out their final survey sheet. If necessary, repeat vitals will be obtained until the Principal Investigator feels that the subject is medically cleared to leave.

8 Statistical Plan

8.1 Primary Endpoint

Each injection will be evaluated by 100mm visual analog scale (VAS) for acute pain immediately after the injection is complete. Patients visually indicate by drawing on paper where their pain is on a 10 cm line, with one end labeled no pain at all and the other worst pain imaginable. The primary endpoint is a statistically significant mean reduction in acute pain on VAS of 10mm or more, per Bijur et al, who determined that this change indicates a real clinical change in acute pain. Quantitative VAS data will be analyzed by a two-tailed t-test, and by linear regression model, incorporating location, and order of intervention (i.e. intervention
first or second).

8.2 Secondary Endpoints

Following the completion of both injections, volunteers will indicate which injection they preferred, with a no preference option included. Patients will also be queried on demographic information after the injections have been completed. They will be asked age, sex, role at University of Pennsylvania. Because pain is characterized as quantitative AND qualitative, include a free response section for comments, specifically asking Do you have any comments on how the kinetic anesthesia device affected your injection experience? A second qualitative entry section will ask: Were you bothered in any way by the VAD [check yes or no] if so please comment. Quantitative VAS data will be analyzed by a two-tailed ttest, and by linear regression model, incorporating location, and order of intervention (i.e. intervention first or second). Quantitative preferential data will be analyzed by logistic regression model incorporating location and order of intervention.

8.3 Sample Size and Power Determination

Sample size was calculated in STATA using the change in VAS needed for clinical significance, in concordance with effect sizes and standard deviations from previous studies. Sample size calculated to detect a clinically significant difference at each of three locations with alpha = 0.05 and a power of 0.8.

8.4 Statistical Methods

Quantitative VAS data will be analyzed by a two-tailed t-test, and by linear regression model, incorporating location, and order of intervention (i.e. intervention first or second). Quantitative preferential data will be analyzed by logistic regression model incorporating location and order of intervention.

9 Safety and Adverse Events

9.1 Definitions

9.1.1 Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

For FDA regulated studies the FDA defines an adverse event as the following:

Adverse event means any untoward medical occurrence associated with the use of a drug in humans whether or not considered drug related.

In this study, the most likely event would be an adverse reaction to lidocaine. In this specific setting, using this dosage of lidocaine the most likely reaction will occur at the local injection site. A systemic reaction would be exceedingly unlikely.

9.1.2 Serious Adverse Event

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

For additional information on definitions and clarifications which may be helpful in creating the safety monitoring portion refer to Appendix 17.7

9.2 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

9.3 Relationship of AE to Study

9.4 Reporting of Adverse Events, Adverse Device Effects and Unanticipated Problems

Investigators and the protocol sponsor (which may or may not be a Penn Investigator) must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible,

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study intervention was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study intervention

Additionally all other events (unanticipated problems, adverse reactions, unanticipated adverse device effects and subject complaints will be recorded and reported with respect to institutional and federal policies as described in the Penn Manual and below.

9.4.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

9.4.2 Data and Safety Monitoring Plan

Data and safety monitoring will be performed by the principal investigator. Monitoring will be conducted per the Lidocaine drug label: "Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patients state of consciousness should be accomplished after each local anesthetic injection." For additional safety precautions, vitals will be also be obtained prior to subject receiving their first injection. Vitals will include heart rate, blood pressure, respiratory rate. Assessment of the participants adequacy of ventilation will also be carried out prior to and after the lidocaine injections.

10 Study Administration, Data Handling and Record Keeping

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10.2 Data Collection and Management

Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study. Paper based records will be input into a secure electronic database and the paper records will be destroyed as soon as is possible.

Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords, and will be kept on password-secured computers.

Wherever feasible, identifiers will be removed from study-related information, with subjects assigned unique non-identifiable study IDs.

Each subject will be assigned a random study ID number, and a key will be used to link this number to their identifiable information. This link will be used only to track adverse events if they occur.

Study data, i.e. visual analog scale ratings, preferences, and demographic information will not be connected with names, birth dates, or MRNs at any time. Data will be collected in this manner on paper and will be immediately encoded in a secure computer database, and the paper records will be kept securely until after the closure of the study with the IRB.

Electronic identifiable information will be stored on the Penn Medicine server and that any paper documents with identifiers (such as consent forms) will be stored in a secure location under lock and key.

Data will be kept on password-protected computers.

A resource at the University of Pennsylvania that can assist you in developing and maintaining data collection and management systems is the Clinical Research Computing Unit (CRCU) in the Center for Clinical Epidemiology and Biostatistics (CCEB) Records Retention

11 Ethical Considerations

11.1 Risks

The main risk of this study is the (expected) discomfort of lidocaine injection in the face and back. Lidocaine is a well-studied and well-tolerated drug. The risks of injecting this dose of lidocaine (0.5mL, 1%) are exceedingly low. The most likely reaction to this dose will be at the site of the injection. Inadvertent intravenous injection is theoretically possible but has not happened in over hundreds of thousands of injections in our clinic while properly anesthetizing skin for cancer removal since 2005. Furthermore, the concentrations and volume injected has an infinitesimal risk of inducing systemic side effects. Adverse reactions to lidocaine will be treated according to standard of care. Study personnel are also well trained in diagnosing side effects of lidocaine toxicity. There will be no epinephrine used in this study (a common additive to lidocaine) - this lowers the chances of an adverse reaction. There are no known risks from application of a KAD at the peri-injection site. Covino BG: Pharmacology of local anesthetic agents. Br J Anaesth. 58:701-716 1986 Walsh A, Walsh S: Local anesthesia and the dermatologist. Clin Exp Dermatol. 36(4):337-343 2011.

11.2 Benefits

Anecdotal evidence claims that local anesthetic injection is the most painful part of minor dermatological procedures. A reduction in the pain of injections by the vibration device would improve the overall patient experience and would be easily generalizable to all patients in the clinic, and possibly patients in outpatient surgical settings. Furthermore, if successful this study would provide evidence based guidelines for the proper use of these medical devices in multiple locations on the body.

11.3 Risk Benefit Assessment

We anticipate that the potential benefits and knowledge to be gained by this study outweigh the potential risks to subjects involved in this research study for the following reasons: Individuals have volunteered to participate and given informed consent to enter the study. They face minimal risk. There are no direct benefits for participation in the study. The knowledge gained will benefit those receiving similar injections in the future.

11.4 Informed Consent Process / HIPAA Authorization

Informed consent will be obtained in writing at the time of the investigative procedure, by the PI and research assistant. Prospective participants, after responding to a recruitment email, will receive a full description of the study procedure, risks and benefits. They will then be able to decide whether they wish to participate in the study. If they choose to participate, subjects will be informed again on the day of the study, and written consent will be obtained at that time. The language used will be targeted for a layman's understanding. This should be well-understood by the target subject population of medical students. It is not anticipated that subjects incapable of consent or those requiring legally authorized representatives will enroll in the study. Participants will be allowed to withdraw from the study at any time by a verbal refusal to proceed.

11.5 Conflict of Interest

No conflicts of interest to report

11.6 Subject Stipends or Payments

For their time and effort of being in a trial, subjects will be compensated $25.00 on a Greenphire Clincard at the end of their completed visit.

12 References

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5. Kuboa et al. Guidelines for the use of local anesthesia in office-based dermatologic surgery. JAAD. 2016;74:6:1201-1219
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7. Reed Michael D, van Nostran W. Assessing pain intensity with the visual analog scale: a plea for unity. J Clinic Pharm. 2014; 54:241-244
8. Walsh A, Walsh S: Local anesthesia and the dermatologist. Clin Exp Dermatol. 36(4):337-343 2011

13 Attachments

The following documents are attached:

- Sample Consent Form

- Cover Letter
- Sample recruitment flyer
- Sample recruitment letter
- Additional device information
- Sample electronic recruiting communication
- Sample of data collection sheet
- Brochures for buffered and un-buffered lidocaine, Sodium Bicarbonate
- Sample of Inclusion/Exclusion criteria data sheet
- Official manufacturers device instructions.

13.1