Mass General Brigham

Novel Cooling Device for Pain Management During Fingerstick Blood Draws

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1. Background and Significance

Patient compliance with laboratory testing is one of the most underrecognized challenges in developing a treatment plan for acute and chronically ill patients. The ability to offer alternatives to standard venipuncture blood draws would greatly increase a laboratory's ability to provide testing to patients and health care providers.[1]

Currently the venipuncture in the antecubital fossa area is the standard procedure for blood collection.[2] Unfortunately, this can be painful and the veins in this area could be hard to access in some patients (including kids).

The fingerstick blood draw has been used as an alternative for calcium and glucose measurements. Capillary blood is used in neonatal population as well.[2]

The procedure of finger-prick blood collection may in some instances cause minor levels of stress and anxiety to individuals as well as acute levels of pain at the time of "prick." [3] We are attempting to reduce stress and anxiety with this new device that aims to avoid the pain of this procedure.

Aiming a less painful, potentially easier alternative we devised a novel that can be applied distally on the digit prior to the blood collection procedure and may provide analgesia through propylene glycol, a liquid coolant that is run through tubes in the device to safely cool tissue to 0°C to 7.5°C to achieve numbing. We hypothesize that this device will safely and effectively reduce the pain associated with the fingertip pricks and increase the amount of capillary blood collected. Besides, we believe in the future this novel could be used for other finger or procedures of the nail unit.

Multiple punctures with a large lancet were a frequent cause of discomfort among patients and should be given consideration since the desire to avoid a painful venipuncture is a common reason given as justification to consider this type of sample.[1] With this new device the discomfort will be reduced by its application followed by the numbness of the finger.

Therefore, capillary sampling should be considered on patients who refuse venipuncture or venous access cannot be established. [1]This method is also considered to be useful for screening of blood disorders.[4]

Iwasawa et al reached a good correlation observed between fingertip and venous blood test values for the 14 biochemical parameters. For example, there was no significant difference in the white blood cells count across specimens, and the fingertip blood collection method allowed them to collect specimens by a single puncture, obtaining consistent results for the blood cell counts.[5]

The study will take place at MGH's Clinical Unit for Research Trials & Outcomes in Skin (CURTIS) at 50 Staniford Street, Suite 240 Boston, MA 02114, or Translational Clinical Research Center (TCRC) on the 12th floor of the White Building.

2. Specific Aims and Objectives

To evaluate a novel tissue-cooling device for pain management during needle sticks and /or blood draw on the fingertips.

The study will use a device developed in conjunction with Sunrise Labs, an experienced medical device development firm (https://www.sunriselabs.com/).

The specific aims of the study are as follows:

Aim 1. Evaluate the pain management capability of the tissue-cooling device for finger prick blood draws compared to standard of care (antecubital venipuncture).

Aim 2. Quantify the amount of blood collected by the finger pricks.

3. General Description of Study Design

This is a self-controlled single-site study of 12 healthy subjects. The novel Cooling Device for Pain Management will be applied to the subject's finger, and a blood draw will be performed. The study includes blood amount quantification and a pain score report to evaluate the pain caused by the prick. Study subjects will be asked to do one visit of approximately 1 hour.

4. Subject Selection

Subjects will be screened to determine if they meet all the eligibility criteria specified below.

We will recruit and screen up to 20 subjects with the goal of having 12 subjects enroll and complete the study.

a. Inclusion/Exclusion Criteria

Inclusion Criteria:

- Signed informed consent to participate in the study.
- Male or Female subjects, ≥ 18 and ≤ 60 years of age at the time of enrollment.
- All Fitzpatrick Skin Types are eligible
- General good health confirmed by medical history and skin examination of the area to be treated
- Subjects fifth finger is 13-23mm in diameter at the distal phalanges.
- Subject must be able to read and understand English.

Exclusion Criteria:

- Subject has had a surgical procedure(s) in the intended area of treatment in the last 6 months.

- Sensitivity to the cold or history of cold-induced diseases including Raynaud's disease and cryoglobulinemia
- Subject has a history of bleeding disorder or is taking any medication that in the investigator's opinion may increase the subject's risk of bruising.
- Suffering from significant skin conditions in treatment areas or inflammatory skin condition, including but not limited to open lacerations or abrasions, hidradenitis, or dermatitis of the treatment area prior to treatment (duration of resolution as per the Principal Investigator's discretion) or during the treatment course.
- History of keloid scarring, abnormal wound healing and /or prone to bruising.
- History of epidermal or dermal disorders (Particularly if involving collagen or micro vascularity) including collagen vascular disease or vasculitis disorders
- Subject is unable or unwilling to comply with the study requirements.
- Subject is currently enrolled or has been enrolled within the prior 3 months in a clinical study of any other unapproved investigational drug or device.
- Any other condition that would, in the professional opinion of the investigator, potentially affect the subject's response or the integrity of the data or would pose an unacceptable risk to the subject.

b. Source of Subjects and Recruitment Methods

The study will be posted on the Rally recruitment website, the Partner's clinical research web page (rally.partners.org/), to reach an economically and socially diverse population.

5. Subject Enrollment

a. Method of Enrollment

All subjects will be subject to a telephone prescreening by study staff before scheduling the initial screening visit. All subjects who sign an informed consent form (ICF) and are screened will be documented on a screening log. All subjects who qualify at the screening visit and who are enrolled in the study will be documented on the enrollment log. A note will be made in the source documentation verifying that the subject has willingly signed the ICF prior to participation in any study procedures.

b. Informed Consent Form (ICF)

A licensed physician investigator will inform the potential study subject of all aspects of the study and answer their questions. Sub-investigators (e.g., nurse practitioner or study staff) may assist in the consent process. If the subject agrees to be a study subject, they will document consent in writing by signing an ICF. Subjects who need more time to decide whether they would like to participate will be given a copy of the consent form and will call if they are interested in participating in the study.

The investigator is responsible for using a consent form that has been approved by the IRB/Partner's HRC and is the most current version. If a new version of the consent form is approved by the IRB/Partner's HRC while a subject is still participating in the study, then the Investigator will inform the subject of the changes and, if the subject agrees to continue study participation, they should sign the updated form.

Written or digital (Adobe E sign) informed consent will be obtained by a licensed physician investigator prior to performance of any protocol-specific procedures.
Only fluent English speakers will be enrolled in the study. Part of the study protocol requires real-time assessment of pain to uncomfortable stimuli. The risks of this study, which does not have any direct benefit for the subject, would outweigh any potential study benefits in this case.

6. STUDY PROCEDURES

a. Study visits and procedures

Screening visit

Screening visit is expected to last approximately 20 minutes.
During the screening visit, the investigator will discuss with each subject the nature of the study, its requirements, and its restrictions.

The following will be performed to determine eligibility:

- Review of inclusion/exclusion criteria
- Medical history and demographics
- Review of medications

Subjects who qualify for the study will be consented by a licensed physician investigator. Subjects who fulfill all inclusion and exclusion criteria may enroll and begin the Visit 1 procedures that same day.

Visit 1

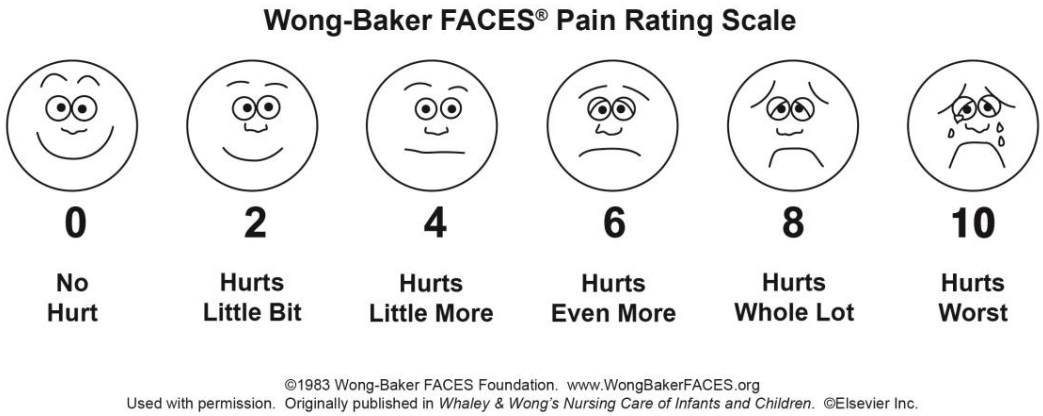
Visit 1 is expected to last approximately 1 hour.

The following assessments will be performed during Visit 1:

- Review of eligibility criteria
    - Ring size measurement
- Review of medical history and medications
    - Urine pregnancy test (for female particpants of childbearing potential)
- Take blood pressure (2 times before treatment; 2 times after) using a standard hospital owned blood pressure arm cuff device.
- The novel digit cooling device will be turned on and allowed to chill to -3 degrees Celsius prior to the procedure.
- Two fingers (one on each hand) will be pricked during Visit 1: the “control” digit and the “chiller” digit.
    - The first finger to be pricked will be randomized.
    - The pricked fingers will be either the fifth or third digit(s).

- Pricks will be administered using a sterile and disposable McKesson Push-Button 17G or 23G Safety Lancet, bought specifically for this trial.
- Subjects will be instructed on how to report a pain score for each prick. A visual 10-point pain scale will be used (see below).
- The procedure for the "control" digit is as follows:
    - A Beurer oximeter will be used to measure the percent oxygen and pulse rate.
    - A thermal camera will be used to measure the temperature of the finger tip.
    - One prick will be applied to the ventral tip of the "control" digit. A pain score will be reported by the subject.
    - The pricked finger will subsequently be held over a single-use Whatman 903 filter paper. Approximately every ten seconds after the prick, the filter paper will be gently applied to the blood drop to absorb the blood. This will be repeated on new locations of the filter paper until blood flow stops. At least one Whatman 903 filter paper will be used per finger prick. The Whatman 903 filter paper will be imaged.
- The procedure for the "chiller" digit is as follows:
    - A sterile glove will be placed on the "chiller" hand. The top of the fifth or third finger of the glove will be cut and rolled down to the base of the finger to promote venostasis and blood harvesting.
    - A Beurer oximeter will be used to ensure there is not enough blood flow to measure the percent oxygen and pulse rate in the finger.
    - A thermal camera will be used to measure the temperature of the finger tip.
    - A layer of glycerol will be applied circumferentially to the intended treatment area on the "chiller" digit.
    - No more than one minute after sterile glove application, the novel digit cooling device will be applied to the "chiller" digit on the area with glycerol.
    - No more than four minutes after the novel digit cooling device is applied to the "chiller" finger, one prick will be applied to the ventral tip of the "chiller" digit. A pain score will be reported by the subject.
    - The pricked finger will subsequently be held over a single-use Whatman 903 filter paper. Approximately every ten seconds after the prick, the filter paper will be gently applied to the blood drop to absorb the blood. This will be repeated on new locations of the filter paper until blood flow stops. At least one Whatman 903 filter paper will be used per finger prick. The Whatman 903 filter paper will be imaged.
- Post-procedure images will be taken of the tips of the "control" and "chiller" digits.
- A thermal camera will be used to video record the fingers starting with the sterile glove application on the "chiller" finger until the post-procedure images have been collected by an encrypted iPhone 12 Pro.
- Regular video recording with an encrypted iPhone 12 Pro will be done simultaneously.

Wong-baker pain assessment on a visual analog pain scale:



- The device will be removed from the digit
- Study staff will document any anticipated side effects or Adverse Events that occur during the study visit.
- A licensed physician investigator will be operating the study device during the procedure.

***First Follow-up Photo** (6-8 days after Visit 1)*

Subject will be asked to send a photo of his treated fingers to MGH security email. The photos must be taken from the fingers and areas where the device has been applied. The photos will be sent by encrypted MGH email.

***Second Follow-up Photo (27-31** days after Visit 1)*

Subject will be asked to send a photo of his treated fingers to MGH security email. The photos must be taken from the fingers and areas where the device has been applied. The photos will be sent by encrypted MGH email.

An optional visit can be requested by the investigator if he cannot evaluate the treated area by the photos of if he believes in person visit is needed for better clinical assessment.

Drugs to be used

No therapeutic drugs will be used in this study.

Devices to be used

Experimental Cooling Device description

The experimental device is a cooling device intended to provide analgesia during needle sticks for blood draws on digits extremities. The device is a circulating fluid chiller using a propylene glycol / water mixture (4:7) flowing through an applicator designed to cool the conductive nerves in the digit to a temperature below which nerve conduction from the distal portion of the digit reduces and/or ceases. The device is designed with two u-shaped coolant tubes that are applied to the circumference of tissue at the base of a digit. The coolant tubes appose each other to surround the digit and then are brought together with a screw /spring mechanism to apply sufficient pressure to the main arteries feeding the digit to partially occlude blood flow, thereby enhancing the tissue-cooling effect.
The clinician monitors tissue blanching while applying the applicator to ensure there is sufficient but not excessive occlusion.

With a circulating coolant temperature of -3°C, the device will cool tissue in contact with and near proximity to the cooling tubes to 0°C to 7.5°C. The subject's hand will be wearing an sterile glove to provide a barrier between the cooling ring and skin. The fifth finger of the glove will be removed sufficiently to expose the area to be pricked in this study. This circumferential ring of cold and partially occlusive pressure on the digit will provide analgesia by blocking nerve conduction signals from leaving the digit and signaling pain to the central nervous system. The pressure on the arterial vessels assists tissue cooling by reducing blood flow and therefore the amount of heat transferred to the cooled tissue.

This device poses no risk to the subject if left on for 10 minutes or less. The device will only be on the subject for 7 minutes, and glycerol will also be used to further decrease any risk to the subject.

Thermal camera

Flir A655SC Thermal Camera A600 Series
A thermal camera will be used to take a video recording of the subjects' "chilled" and "control" hands during the first study visit to detect temperature differences of the treatment area. Video recording will start before the device's application and will continue until the post-procedure pictures have been taken. The device will be removed, and thermal images of the treatment area will be obtained.

Video Recording
An encrypted iPhone 12 Pro camera will be used by study staff (investigator or research coordinators) to take a video recording from the subjects' chilled hand during the first study visit. Video recording will start before the device's application and will continue until the post-procedure pictures have been taken.

Videos will be blindly reviewed by a physician and assessed using temperature grading scale. All video recording data files will be labeled with the study subject number. No identifying information will be used in labeling the video data files and the files will be stored on Partners Dropbox. The videos will be stored at Partners Dropbox until 7 years after the end of this study when all the copies will be permanently deleted from this drive. Only study staff will have access to the videos (for storage purposes- like research coordinators or for assessment - investigators).

b. Data to be collected and when data is collected

Study data will be collected during screening and study visit. Study data to be collected includes Subject's reported pain scores with Wong-Baker pain rating scale, subjects' oximeter readings, subjects' video recording, subjects' photographs, and photographs of the Whatman 903 filter papers containing subjects' blood drops.

c. Remuneration

Subjects will receive $150 for completing Visit 1. The total remuneration amount will be $ 150 for completion of all study visit.

We will also provide a parking voucher for each visit upon request.

7. Risks and Discomforts

a. Complications of prick procedure

The complications of prick include pain, swelling, edema, redness, and bruising.

b. Device complications/malfunctions

The device is designed to apply pressure to the two main feeder vessels to the digit. The pressure applied is controlled by the study physician who will monitor tissue blanching based on their clinical experience to ensure an appropriate amount of pressure/occlusion. In addition to monitoring pressure through tissue blanching, this study will limit the amount of time the device can be applied to the digit to 5 minutes. This time limit will be sufficient to prevent tissue ischemia, especially with the tissue cooling that will also be applied.

The device is designed to circulate propylene glycol cooling fluid at -2.5 degrees C. There are temperature indicators on the inlet and outlet tubing to the finger chiller. Temperature indicators will be checked and confirmed to be at the correct operating temperature prior to applying the device to subjects and during the finger pricking procedure.

If there were a leak of cold propylene glycol onto a subject's or study staff's skin, the temperature of the cooling fluid is not cold enough to cause significant damage. The propylene glycol portion of the cooling fluid in the system is a food-grade propylene glycol conforming to United States Pharmacopeia standards and is GRAS. According to the safety data sheet, it is considered to have low toxicity and may cause mild skin irritation. If the system is found to be leaking cooling fluid during the study, study staff will immediately remove the device from the subject and wipe the leaked fluid from the subject's or staff's skin. Study staff will clean the affected area in accordance with standard cleaning procedures for intact skin.

The circulating fluid is chilled and pumped by a commercially available liquid chiller. If the chiller fails to maintain the circulating fluid temperature or if the pump stops pumping fluid, the temperature of the finger cooling device may rise, the device may not provide sufficient analgesia to the tissue and the subject may feel pain. If the chiller fails to main the -2.5 temperature or the pump fails to circulate the fluid, the inlet and outlet temperature sensors near the clamp will rise, providing feedback to the

clinician to stop the experiment. Subjects will be instructed by study staff to immediately report any pain to the study physician performing the treatment. The subject has the right to stop the study at any time if they feel pain or otherwise wish to stop the study.

c. Psychosocial (non-medical) risks

There is a potential risk of loss of privacy. We will protect privacy by labeling samples, information, and data files only with a study subject number code and keeping the key to the code in a password protected database.

8. Benefits

a. Potential Benefits to subjects
There are no medical or health benefits to subjects for participating in the study.

b. Potential Benefits to Society
Information gathered from this study may improve pain management during blood draw for patients in the future and improve our understanding of new ways to provide analgesia to the skin without topical or injectable numbing medication.

9. Statistical Analysis

Pain Scoring Analysis
The Wong-Baker FACES Pain Rating Scale will be used to score subject pain in visit 1.

Statistical methods

The study is intended to gather empirical data about the pain assessment of the treatment area. Descriptive statistics will be collected to present quantitative descriptions of the pain level comparisons between the two hands.

In order to achieve a power of 0.95 with a p-value < 0.05, a sample size of 16 subjects is needed. This is assuming a standard deviation of 2 on the Wong-Baker Pain Rating scale, which will be used as the primary clinical outcome measure. A two-sided, independent t-test will be used to determine if any significant statistical difference is present between the pain level of each treatment arm using the absolute difference between the control and experimental pain scores.

10. Monitoring and Quality Assurance

a. Independent monitoring of source data

Experienced study personnel (study monitor) who are not assigned to complete procedures of this study will conduct monitoring after the first subject is enrolled and periodically thereafter. The monitor will be responsible for confirming the completion and correctness of the study procedures as well as record collection and keeping.

b. Safety monitoring

Prior to enrollment, subjects will be screened for eligibility; at which time a complete medical history, including a baseline assessment of the subject's skin will be done. Evaluations will be ongoing throughout the study to detect adverse events and changes in existing medical conditions.
At any time after enrollment, a subject may be discontinued. Reasons for discontinuation of a subject from the study will include, but may not be limited to, the following:

1. Subject is found to be intolerant to a required study procedure at any time point.
2. Subject is noncompliant with protocol restrictions and requirements.
3. Subject develops an intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
4. Subject becomes pregnant while participating in the study.
5. Subject enrolls in another investigational study.
6. Subject requests to withdraw from the study.
7. The study staff decides to suspend or terminate the study.

If possible, a final set of assessments will be performed on all subjects who end their participation prior to study completion.

c. Outcome monitoring

The study will be conducted in accordance with applicable regulations and Good Clinical Practice Guidelines. Keeping files locked with access limited to study staff will ensure confidentiality and data integrity.

d. Adverse Event Reporting

Definition

Adverse Event (AE) is any untoward medical occurrence in a subject that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Serious Adverse Event (SAE) is any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is another medically important condition

Reporting and Documenting Adverse Events
All untoward medical occurrences that occur after the subject signs a consent form will be documented as an AE. The Investigator will ensure that all events that occur during the study period are recorded. All AEs will be followed until resolution or until, in the Investigator's judgment, they are chronic and stable. If an emergency situation should occur, appropriate medical measures should be taken to stabilize the subject.

Documentation of AEs includes date and time of onset and resolution of AE, intensity, frequency, seriousness, related interventions, and outcome. The Investigator will also evaluate the probability of a causal relationship of the AE to the study treatment as being: "definite, probable, possible, unlikely, or unrelated." Intensity of adverse events will be graded as mild, moderate, or severe according to the following criteria:

- Mild: symptoms that are easily tolerated and transient in nature with minimal or no impairment of normal activity
- Moderate: symptoms that are poorly tolerated, are sustained, and interfere with normal activity
- Severe: symptoms that are incapacitating and render the subject unable to work or participate in many or all usual activities

All SAEs will be reported to the IRB according to the IRB's requirements.

11. Privacy and Confidentiality

INSTRUCTIONS
Delete grey Instructions box upon completion of this section

- Select the Privacy and Confidentiality measures that apply to this research by checking the box next to each statement (Check all that apply)
- Note that not all of the measures outlined below may apply to your study
- Do not delete statements that do not apply to your study; leave the boxes unchecked
- Describe any additional privacy and/or confidentiality measures that are not captured by the check box items in free text following the check boxes

☒ Study procedures will be conducted in a private setting
☒ Only data and/or specimens necessary for the conduct of the study will be collected
☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
☒ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies
☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
☒ Additional privacy and/or confidentiality protections

12. Data Management

a. Data collection

All study data will be collected during study visits. Pain scores will be recorded on the case report form for visit 1. All physical documentation and IRB correspondence will be stored in study binders maintained in restricted lab space only accessible by study staff and members of the Manstein Lab.
Digital data including photographs and video recording will be deidentified and stored on MGB computers. Any identifiable information in photographs tattoos will be blacked out and deidentified. Subjects' faces will not be recorded. All study documents containing PHI will be password encrypted, including the enrollment log and identification key. An encrypted external hard drive will be used to store the data as a backup.

b. Record retention

The Investigator or designees will retain all study records in accordance with the test facility's SOP's.

13. IRB Review and Approval

The study will not begin prior to the receipt of written confirmation of approval by the IRB and any relevant regulatory authority. It is the responsibility of the Investigator to obtain the IRB approval (per the U.S. Code of Federal Regulations, Title 21, Part 56, and applicable ICH guidelines) for the protocol, amendments, informed consent, subject information sheet, questionnaires, and advertising materials used to recruit study subjects, if appropriate.

14. References

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