Clinical Trial Protocol

Title: Determining the Variable Factors in Cutaneous Perception of Vibratory Stimulation

Principal Investigator: Bryan T. Carroll, MD, PhD
Department of Dermatology
University of Pittsburgh School of Medicine
3601 Fifth Ave, Suite 6a
Pittsburgh, PA 15222
carrollbt@upmc.edu

Co-Investigators: Panayiota Govas, MD, MScMed
Rashek Kazi, MD, PhD
Rachel Slaugenhaupt

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Study Title: Determining the Variable Factors in Cutaneous Perception of Vibratory Stimulation

Short Title: Variable Perception of Cutaneous Stimulation

1. **Study Objective:**

   Determine how patients in an out-patient dermatologic surgery setting interpret non-noxious stimulation, specifically focusing on vibration.

2. **Specific Aims**

   Perception of cutaneous stimuli is critical in the diagnosis and treatment of many dermatological diseases. However, there is little understanding of how global sensations varies across populations.

a. *Specific aim 1*: Variable perception and interpretation of a non-noxious stimulus.

   Hypothesis: Different patient populations will show subtle, if any, difference of non-noxious stimulation.

   Rationale: Historically, there is evidence citing differences in perception of acute noxious stimuli across age, history of exposure to pain, and gender. Little information is available regarding non-noxious stimuli. In previous work from our group and validated by other researchers, patients are largely able to tolerate the non-noxious stimulation of vibration. Our aim here is to determine whether this tolerability and interpretation shows any difference across cohorts, specifically those in an outpatient surgical setting.

b. *Specific aim 2*: Variable perception and interpretation of a noxious stimulus following a non-noxious stimulus

   Hypothesis: Different populations will show a significant difference in perception of noxious stimulation

   Rationale: As previously cited, different cohorts of humans has a wide variety in how pain, both acute and chronic, is perceived. In this aim, we can identify how the noxious stimulus of an injection of anesthetic varies across populations in an out-patient surgical setting. Further, it is known that the application of vibration prior to needle injection significantly reduces the pain felt by the patient. This aim can determine how this change varies across different patient cohorts.

c. *Specific aim 3:* The level of pain anticipation will vary by individual and will predict pain outcome.

   Hypothesis: Patients who anticipate greater pain will experience greater perceived pain than those who do not. Vibration during anesthetic injection will reduce pain in all patients, regardless of anticipatory pain score.

   Rationale: Surgical patients who anticipated pain > 40 mm on the visual analog scale (VAS) reported a significant increase in acute post-surgical pain (APSP) compared to non-catastrophizers (VAS ≤ 4) on all post-operative days (1).

3. **Background and Rationale:**

   Previous work has quantified the effects of using non-noxious stimuli, specifically vibration, in reducing the pain of procedures. Work from the project PI Bryan T. Carroll (2), as well as Kenneth Beer (3), have detailed the ease and practical use of handheld vibration devices during in office procedures. Several other studies have also noted improved patient comfort with noxious stimulation after applying brief vibration. This has been studied in in office lip filler injection (4), botulinum toxin (5), and lip augmentation (6). Further, these studies have shown that not only does the approach provide significant analgesic control, patients opt to repeat use of vibration in future procedures at a rate of over 90% (6).

   Mechanistically, the basis for this approach lies in the "gate-control of pain" theory. Established by Melzack and Wall, gate-control theory postulates that non-noxious stimuli such as vibration are detected by a specific subset of cutaneous nerve fibers known as a-beta fibers (7). This signal is rapidly transferred to the central nervous system and processed. By activating these fibers, there is a second set of signals which inhibits the

activation of another set of cutaneous nerve fibers known as A-delta and C fibers. These fibers normally transmit painful signals, both acute and chronic. Through this activation-inhibition model, we intend to effectively limit the degree to which noxious stimuli is felt in the outpatient procedural setting (8).

4. Significance

Currently, there are several avenues requiring further detail bringing significance to this study. The overall aim is to eliminate the pain experienced by patients during outpatient surgical procedures. There are over 300 million in office procedures in the United States alone necessitating injections of anesthetic. The discomfort of this process leads to many patients actively neglecting potentially life-threatening disease to avoid the process of anesthesia. This consistent across many different populations. As such, our main goal is to minimize the discomfort associated with in office procedures, specifically the application of anesthetic. Our studies heavily rely on the "gate control" theory of pain proposed by Melzack and Wall, which translates to the decrease of the intensity of pain by concurrent transmission of unpainful stimuli, such as vibration (7). Currently, vibration alone is unable to meet this need. As such, more information is needed on the specific details surrounding this non-noxious stimulus. Our study will define how this perception is "felt" in an objective manner. This will allow future work to better optimize how vibration is applied to the skin.

Second, while data in general has shown that vibration preceding a noxious stimulation reduces the sensation of pain, there is no understanding of the variability by which this occurs. As such, we aim to use a larger and broader population than has been previously detailed to better understand the differences between various cohorts. This will allow for optimization of pain control and minimization in office discomfort.

5. Study Population

a. Inclusion Criteria
   i. Age 18+
   ii. Male and Females
   iii. Patients presenting for cutaneous cancer removal surgery with Dr. Bryan T. Carroll at UPMC Falk Dermatologic Surgery Clinic

b. Exclusion Criteria
   i. Age < 18
   ii. Non-English speaker
   iii. Difficulty following protocol
   iv. Participants who did not undergo surgical procedure

6. Study Design & Procedure

Day of procedure: Patients that expressed interest in the study at their pre-operative phone call will again be asked about their interest in participating in the study (Appendices II & II)

a. Pre-operative research activities:

   i. Consented participants will be randomized to vibration or no vibration.

      For randomization into study group: We will use a Gaussian random number generator (available at available at https://www.google.com/search?q=random+number). It will generate a number (0 or 1). If 0, this will be for the control group (device placed on skin in OFF mode), if 1, this will be in the test group (device placed on skin in the ON mode).

   ii. They will be given the pre-operative questionnaire by an investigator to complete before they are prepared for surgery (Appendix IV)

iii. Once the patient arrives in the procedure room the clinician will discuss the device and how it works. The device is a 10cm handheld battery-operated device. Manufacturer: Finever. It can be purchased over the counter. When on, the VAD is on it oscillates at a rate of approximately 100 Hz. This feels similar to the sensation of holding an electric hair trimmer.

b. Intraoperative research activities (Appendix V):

i. The VAD will be placed on the skin in both the ON and OFF modes at a site distant from the test/procedure site.

ii. Number of exposures to VAD: maximum of 2 exposures

iii. As detailed in the protocol, the patient will report their pain score at various time intervals which will be recorded on the research operative data collection sheet

c. Post-operative research activities:

4-6 hours after the procedure the clinician investigator will call the patient to administer the post-operative pain questionnaire (Appendix II).

d. Duration of procedures:

The total time that a participant will be in the study is no more than 12 hours. This includes time of consent to the post-operative call.

Timeline of study procedures

i. Participant to be informed of study via phone (2-3 days before procedure)

ii. Participant will arrive for procedure, go through the consent process, and complete a questionnaire (1 hour)

iii. Participant will complete the research part (vibration) of the study during the standard of care procedure (1-2 hours)

iv. Post-procedure follow-up by co-investigators (Panayiota Govas, Rachel Slaugenhaupt) about 4-6 hours post-op (15 minutes)

e. Personnel

The application of the device will be performed by the PI (Bryan T. Carroll). Data acquisition, patient follow-up, and further writing and analyses will be performed by the PI (Bryan T. Carroll) and/or the Co-Investigators (Panayiota Govas, Rashek Kazi, or Rachel Slaugenhaupt).

Information regarding the study and administration of pre-study questionnaire will be given by Co-Investigators (Panayiota Govas, Rashek Kazi, or Rachel Slaugenhaupt). Any questions from the study participants will be handled by the PI (Bryan T. Carroll) and/or the Co-Investigators (Panayiota Govas, Rashek Kazi, or Rachel Slaugenhaupt).

7. Data Collection and Reporting

a. Primary Outcomes Measures

The primary outcome measure is pain score using the 11-point numeric rating scale (NRS) pain during multiple time points. This measure will be compared between the VAD ON and VAD OFF groups.

b. Secondary Outcome Measures

The secondary outcomes measure is the anticipated pain measured with the 11-point NRS. A patient questionnaire will be used to collect analgesic patient data (Appendix IV). Both these variables will be compared between the VAD ON and VAD OFF groups.

A minimum clinically important difference (MCID) and substantial clinically important difference (SCID), defined as a relative pain score reduction of ≥ 22% and ≥ 57%, respectively, will be used to assess relative change in NRS pain scores. (7)

8. Data Disclosure and Subject Confidentiality

The research intervention will be conducted in a private room; the collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected, drapes or other barriers will be used for subjects who are required to disrobe.

All data will be stored on a UPMC server behind a firewall in a password protected spreadsheet only accessible to the PI and co-investigators. Data will be discarded 7 years following data collection.

The patient assessments and interviews will be conducted in the clinic in an exam room. Medical information collection will be conducted in the patient's room and the information collected will be limited to that information required to conduct this study. All information acquired, including patient provided information and data gathered during the study, will be collected on a research form that utilizes a study identification number only. At no point will patient health records be accessed for the purposes of this study.

All measures to ensure that the subject's privacy is maintained will be implemented. The information collected will be kept in a secure location with restricted access in order to assure the data will remain confidential. The study ID record will be kept in a separate, secure location. The data will be collected in a de-identified fashion and no identifiable medical record information will be maintained on the surveys. Information collected will be kept indefinitely. All information is maintained in a secure area with limited access in a locked cabinet. Computers are password protected.

Although we do not currently have plans to share any of our data, should we decide to share data in the future we will contact the Office of Research before sharing de-identified research data and/or materials to determine whether an agreement needs to be executed.

9. Safety Assessment

Although the study is designed to assess for pain, we reiterate that the painful stimuli of the project is expected to be no more than the pain of the standard of care procedure.

a. Vibration device:

All patients will be pre-empted regarding the risks of the vibration device and as such, any patient is aware of the procedures and is aware they can opt out at any time.

If a patient is notably in pain but not communicating it, the observer will stop the procedure and discard all data.

b. Data Collection:

Once the subjects have been identified and consented. These consents will be stored in a secure location in a locked file which can only be accessed by authorized study staff.

Data collection form will contain a unique study identification number. The linkage list containing the study identification numbers will be stored in a separate locked cabinet. All study related material will be maintained

in a secure area in a locked cabinet with limited access. Access will be limited to persons directly involved in this research study.

c. Questionnaires:

If a patient feels uncomfortable or embarrassed answering some of the questions they will be instructed that they can skip the concerning question.

The investigators will meet monthly to discuss study progress and issues related to patient safety and data management. Problems with subject recruitment or issues concerning subject confidentiality will also be addressed at the monthly meetings. The occurrence of adverse events will be monitored on an ongoing basis for the duration of the study. If a serious or unexpected adverse event occurs, it will be reported immediately to the IRB of the University of Pittsburgh. If an unexpected adverse event occurs, the investigators will re-assess the risk/benefit ratio of the study and submit any modifications deemed necessary to the IRB for approval.

The principal investigator will conduct an evaluation of the progress of the research study on a monthly basis including assessments of data quality and timeliness; participant recruitment, accrual and retention; and a review of outcome and adverse event data to determine whether there is any change to the anticipated benefit-to-risk ratio of study participation and whether the study should continue as originally designed, should be changed, or should be terminated. A summary of these reports will be submitted to the University of Pittsburgh IRB as part of the annual renewal.

10. Statistical Considerations

All values collected will be analyzed to report mean values +- standard deviation and/or standard error from mean. For intergroup comparison analyses, student's t-test, ANOVA and multivariate analysis will be used. Significance will be set at a threshold of $p < 0.05$.

This is a single center/cite study. We have a single variable testing for differences in perception based on type of stimulus. This will entail two measurements.

We are aiming for a power of 0.95 with an alpha of 0.05, for a 2-sided analysis. If we assume that the baseline NRS score will average a mean of 0.5, SD of 1.7 (a clinically significant difference in NRS score has been calculated to be a difference of 2.8) (9). This results in a sample size of 10 (if alpha is set to 0.01, sample size is 14).

As per Ferreira-Valente et. al 2011, parameters of power = 0.80, alpha = 0.05, and SD of 2.2 were defined, and a sample size of 5 was calculated to detect differences in NRS score (10). Similar numbers are calculated for our study using those parameters.

11. Study Site

UPMC Falk Dermatologic Surgery Clinic
3601 Fifth Ave, Suite 6a
Pittsburgh, PA 1522

12. References

1. Sommer M, de Rijke JM, van Kleef M, et al. Predictors of acute postoperative pain after elective surgery. *Clin J Pain.* 2010;26(2):87-94.

2. Gresham, Katherine A. MS; Carroll, Bryan T. MD, PhD. A Simple Elastomer-Pad Vibratory Dampener to Maximize Pain Control of Injections in Patient's Undergoing Dermatological Surgery. Dermatologic Surgery: June 2016 - Volume 42 - Issue 6 - p 788–790

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4. Sharma P, Czyz CN, Wulc AE. Investigating the efficacy of vibration anesthesia to reduce pain from cosmetic botulinum toxin injections. Aesthet Surg J. 2011;31(8):966-971.

5. Mally P, Czyz CN, Chan NJ, Wulc AE. Vibration anesthesia for the reduction of pain with facial dermal filler injections. Aesthetic Plast Surg. 2014;38(2):413-418.

6. Guney K, Sezgin B, Yavuzer R. The Efficacy of Vibration Anesthesia on Reducing Pain Levels During Lip Augmentation: Worth the Buzz?. Aesthet Surg J. 2017 Oct 1;37(9):1044-1048. doi: 10.1093/asj/sjx073.

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9. Farrar JT, Young JP, Jr., LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain. 2001;94(2):149-158.

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13. Approval Letter

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Ground Level
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

To: Bryan Carroll, MD, PhD
From: IRB Office
Date: 6/28/2018
IRB#: MOD17110134-03 / PRO17110134
Subject: Determining the Variable Factors in Cutaneous Perception of Vibratory Stimulation

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The University of Pittsburgh Institutional Review Board reviewed and approved the requested modifications by the expedited review procedure authorized under 45 CFR 46.110 and 21 CFR 56.110.

Modification Approval Date: 6/28/2018
Expiration Date: 4/15/2019

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

APPENDIX I: Pre-operative Phone Script

Pre-op phone call Script

[After all the discussion regarding the case has completed]

Hi Mr./Mrs. _____. My name is _____. I am calling from the Dermatologic Surgery office at UPMC where you are set to have your Mohs procedure on _____. How are you today?

Dr. Carroll is conducting a study aimed to increase your comfort on the day of your visit. We want to introduce the study to you now before the day of surgery so that you can fully consider participating in this study. We will more fully discuss the study at your check-in during your day of surgery.

We use vibration to maximize your comfort. We are testing the vibration we currently use in our clinic. This means that your care will not be changed in any way. Our goal is to further increase your comfort during injections.

You have the opportunity to help us with this study, if you choose to volunteer.

Should I continue?

Let me tell you more about the study. To perform your procedure, we need to inject some pain relief into your skin. We are studying the vibration we currently use on your skin prior to the injection. We will ask you questions during the vibration about the level of comfort you are feeling before, during, and after the injection.

All of your information is kept confidential. All we require is the completion of a short questionnaire, consent form and the questions we ask you during the study. This study is completely voluntary.

Do you have any questions?

If they do: I can forward them to our physicians. The physicians will also be able to answer any questions on the day of your procedure as well.

Would you be interested in helping us with this study? You can back out at any time.

Thank you again!

APPENDIX II: Trial Day Scripts

a. Intro to study/recruitment

Thank you for choosing UPMC Dermatology! We are conducting a study aimed to better understand how patients sense touch on their skin. You have the opportunity today to help us with this study if you choose to volunteer.

To participate, we ask that you sign a consent form and then complete a brief information questionnaire which consists of a few personal and health-related questions. This will allow us to gather the data needed for the study.

More details will be discussed in the examination room.

Remember, you may choose to withdraw yourself from the study at point, there is no pressure.

Thank you again!

b. In patient room

The study entails application of a small device on the surface of your skin where you are having your procedure. The device will apply a small amount of vibration to your skin. The questions we need you to answer are:

1. What is the sensation you feel on your skin?

2. Is that sensation uncomfortable or bothersome?

3. At different time intervals, we will ask how much pain you are feeling.

Pain is rated on a scale from 0-10 with 0 being your baseline and 10 being the worst pain imaginable. Moving forward we will refer to this number as your ***"pain level".***

We will ask you to **keep your eyes closed** during the study so that we can make sure other factors that may influence your pain level are taken away, for example watching the procedure site.

This entire study will last no more than five minutes.

c. Post-procedure script (4-6 hours post procedure)

After all routine post-procedure questions are complete:

1. *Do you recall being a part of the study this afternoon?*
2. *At the site of the procedure, what is your pain level right now?*
3. *Thank you for participating in our study, if you have any questions or concerns moving forward*

please contact us. Further, if you wish to have yourself withdrawn from the study please let us know.

APPENDIX III: Participant Study Documents Checklist

Subject ID: _____

Please mark each box as the task is completed and record the date on which it occurred for the individual patient.

☐ Patient was given information regarding the research study during their pre-operative phone call and expressed interest in participating.
Date: _____

☐ Patient was introduced to the study when arrived and completed the pre-operative questionnaire.
Date: _____

☐ Consent form signed by patient.
Date: _____

☐ After-visit phone call performed, and answers recorded.
Date: _____

Completed by researcher

APPENDIX IV: Pre-operative Participant Questionnaire

Subject ID	
Age	
Gender	**M or F**

1. Currently using any of the following medications on a regular (i.e. daily) basis? (Circle Yes or No)

Circle	**Type of Medication**	**How often? What dose?**
Yes or No	Opiate/Narcotic Medication (oxycodone, morphine, dilaudid, etc.)	
Yes or No	Prescription-strength non-steroidal anti-inflammatory (naproxen, celecoxib, indomethacin, etc.)	
Yes or No	Tramadol	
Yes or No	Ibuprofen (Advil) / Naproxen (Aleve)	
Yes or No	Aspirin	
Yes or No	Tylenol (Acetaminophen)	
Yes or No	Gabapentin	
Yes or No	Anti-depressant	

2. Please indicate the degree of pain you feel at the site you are having treated today. On a scale of 0 to 10, with 0 being no pain at all and 10 being the worst pain imaginable.

0 1 2 3 4 5 6 7 8 9 10

3. Please indicate the degree of pain you expect to feel at the site you are having treated today. On a scale of 0 to 10, with 0 being no pain at all and 10 being the worst pain imaginable.

0 1 2 3 4 5 6 7 8 9 10

APPENDIX V: Participant Training, Study Protocol & Data Collection Sheet

Subject ID: _____ **Site: _____**

Part 1

With nothing on the patient's skin, ask

What is your pain level right now?

Document score

At this point make sure to have a watch or timer at your side, timing is important.

Please close your eyes

About 5 cm from the surgical site, apply the vibration tool **when it is OFF**

Do you feel something on your skin?

At 5 seconds: *What is your pain level?*

At 15 seconds: *What is your pain level?*

Remove device

After 5 seconds, with nothing on skin at the same site as above

Can you please describe the sensation you felt on your skin? Was it vibrating or still?

What is your pain level right now?

OFF	**Describe**	**rest**	**5s**	**15s**	**post**

Device is turned ON then immediately applied to skin

Do you feel something on your skin?

At 5 seconds: *What is your pain level?*

At 15 seconds: *What is your pain level?*

Remove device

After 5 seconds, with nothing on skin

Can you please describe the sensation you felt on your skin? Was it vibrating or still?

What is your pain level right now?

ON	**Describe**	**rest**	**5s**	**15s**	**post**

Part 2 (performed at time of first injection)

- Half of the patients will perform this part with the device on, half will perform with the device off.
- They will be blinded to whether it is on or off, the experimenter will not be blinded.
- A random number will be provided on the patient data sheet, either 0 or 1.

0 = VAD off
1 = VAD on

- *This is the second part of the study, we will apply the device to your skin at the site of the first injection for 5 seconds, then ask for a pain level.*
- *Then after an additional 10 seconds we will perform our needle injection. Then we will ask for your pain level at the time of injection, are you ready?*

Apply the device:

At 5 seconds: *What is your pain level?*
At 15 seconds: perform injection, immediately after: *What is your pain level?*

After all numbing is complete, ask:

Can you please describe the sensation you felt before the injection was performed? Vibration or nothing?

What is your pain level now?

Thank you for participating in our study!

		Describe	**rest**	**5s**	**15s**	**post**
Testing Site	**ON or OFF**					

If OFF, then AFTER VIBRATION: "Is it better now?"	**YES or NO**										
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

APPENDIX VI: Post-Operative Survey Sheet

Date:_____

Patient Number	Time of Procedure	Recall being part of study?	Pain level at this time?
		YES or NO	0 1 2 3 4 5 6 7 8 9 10
		YES or NO	0 1 2 3 4 5 6 7 8 9 10
		YES or NO	0 1 2 3 4 5 6 7 8 9 10
		YES or NO	0 1 2 3 4 5 6 7 8 9 10
		YES or NO	0 1 2 3 4 5 6 7 8 9 10
		YES or NO	0 1 2 3 4 5 6 7 8 9 10