TITLE: Variable Perceptions of Cutaneous Stimuli
PRINCIPAL INVESTIGATOR: Bryan Carroll, MD, PhD
CO-INVESTIGATORS: Rashek Kazi, MD, PhD; Panayiota Govas, M.D., M.Sc.Med
NCT: NCT03467685
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Scientific Background

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 Carroll (1) as well as Kenneth Beer (2) 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 (3), botulinum toxin (4), and lip augmentation (5). 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% (5).

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. 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 (6).

1. 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

2. Beer, Kenneth R. MD. Commentary on a Simple Elastomer-Pad Vibratory Dampener to Maximize Pain Control of Injections in Patients' Undergoing Dermatological Surgery. Dermatologic Surgery: June 2016 - Volume 42 - Issue 6 - p 790.

3. 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

4. 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.

5. 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.

6. Dickenson AH. Gate control theory of pain stands the test of time. Br J Anaesth. 2002;88(6):755-757

Study Objectives

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

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.

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.

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.

Study Design and Methods

This is a DESCRIPTIVE, RANDOMIZED, partially blinded study.

Study design

A randomized, partially-blinded, parallel-group clinical study of perception and interpretation of a non-noxious vibration stimulus compared to placebo (vibratory device in "off" mode) during syringe-mediated local cutaneous infiltration of anesthetic was performed. The protocol was approved by the University of Pittsburgh Institutional Review Board (PRO17110134) and conforms to the ethical guidelines of the Declaration of Helsinki.

Participants

All adults (18+) presenting for MMS, surgical excision, and/or other cutaneous cancer removal surgery at Falk Dermatologic Surgery Clinic affiliated with the University of Pittsburgh Medical Center (UPMC) were eligible for inclusion. Subject enrollment occurred during a 90-day period from April to June 2018. Eligible subjects were informed of the study 24-72 hours before treatment via phone call.

Patients with expressed interest in the study were given more information on the day of study, including the risks and benefits of participating. Any subsequent questions were answered at this time. All participants were given a pre-procedural questionnaire and provided written informed consent. A follow-up phone call was conducted post-procedure.

Participant Training

Participants underwent a training session to answer trial questions ("What is your pain level?") using the 11-point Numeric Rating Scale (NRS) as well as descriptive adjectives of sensation ("Can you describe the sensation you felt on your skin?"). The vibratory anesthetic device (VAD) was placed on a 'training site' approximately 5 cm away from their treatment site

in the OFF mode for 15s (Figure 1). Participants were then asked to describe the sensation they felt on their skin as well as the NRS pain level experienced. This process was repeated with the VAD in the ON mode.

During this time, patients who were unable to discern between the VAD ON and OFF modes, expressed NRS>0, could not communicate effectively, had a language barrier or were unable to follow instructions were excluded (Figure 2).

Intervention

The VAD is a 10cm, handheld, battery-operated device by Finever. When ON, the device oscillates at a continuous frequency of 100Hz. It is non-experimental and available for purchase over-the-counter. The device was customized by positioning a cotton ball at the tip with subsequent placement into a nitrile glove.

The VAD, anesthetic injection and infiltration, and surgical procedure were all performed by a single, board-certified dermatologic surgeon (BTC). The anesthetic used in all cases was lidocaine hydrochloride 1% with epinephrine 1:100,000 and buffered with 8.4% bicarbonate 1:10 (Hospira Inc.). The anesthetic was prepared and administered in a 3 ml syringe with a 30-gauge needle. Anesthetic was prepared the day of the procedure.

Outcome measures

Subjects' pain was assessed using the validated 11-point NRS (0 = no pain, 10 = worst pain imaginable). Pain level was evaluated at multiple time-points; pre-anesthetic injection with stimulus (VAD ON/VAD OFF) at 0s and 5s; the timepoint of anesthetic injection at 15s (NRS) with stimulus (VAD ON/VAD OFF); and 5s post-infiltration with no stimulus present. Patients communicated their pain level verbally at the above timepoints.

Relative change in NRS was calculated with the below:

$$Relative\ Change = 100 * \frac{NRS_{Initial} - NRS_{Final}}{NRS_{Initial}}$$

From the findings of Olsen et al., MCID and SCID was defined as a relative change of 22-56% and ≥57%, respectively.

CONSENT TO PARTICIPATE IN A RESEARCH STUDY
TITLE: Variable Perceptions of Cutaneous Stimuli
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Contact Information: (412) 864-2660

Why is this research being done?
The purpose of this study is to determine if the use of a vibration tool immediately before injection of anesthetic alters your feeling of pain during an injection.

You are being asked to take part in this research study because you are a patient of Dr. Carroll's who has been diagnosed with a skin cancer and are scheduled for excisional or Mohs surgery for treatment.

If you decide to participate a study investigator will give you a questionnaire to provide baseline information about your medical history, it can be completed in the waiting room in under 20 minutes. As part of your normal care you will be prepared for your surgical procedure. The only change to normal care would be right before you receive your anesthetic injection we will randomize (like the flipping of a coin) you to one of two groups. Group 1 will receive a small vibration with a handheld device that is applied to the skin for about 15 seconds Group 2 will have the device applied without vibration. During your procedure we will ask you to rate your pain level about 6 times. We will call you about 6 hours after the procedure and ask a short questionnaire, in addition to our normal postoperative questions.

This is a very low risk study, but you should be aware of risks. There are standard risks with surgery. These will be explained to you along with your consent for surgery.

There is also a risk of mild discomfort from the handheld vibration anesthetic device, however there is no evidence of this being the case. If at any point the vibration becomes intolerable, you can ask us to stop.

The questionnaire will ask questions about your overall health, level of pain tolerance, and your use of pain medication, including opiates. This has a risk of being potentially embarrassing in terms of the social stigma related to such medications and expectations of pain tolerance. As a reminder, all answers will remain confidential.

Any time information is collected, there is a small risk of breach of confidentiality. Your research data will be identified by a unique study number rather than your name and all measures allowed by law to protect your confidentiality will be taken by the research staff. This data will be protected behind a password protected firewall on UPMC servers. It will only be accessible to the above investigators.

This study may not have any direct benefit for you today however the information will be used to understand which populations of patients may require additional support to reduce the pain associated with minor surgical procedures.

Previous research has shown that some patients find a reduction in the pain of injection when the vibration tool is used. However, there is no guarantee that this will be the case for you. You will not be paid for participating in this study nor will your insurance company be billed for the research procedures if you agree to participant in this study. Research use of the data collected may lead to new inventions or products, but you will not receive any money or compensation from any inventions or products that might be developed in the future. There are no current plans to share the research data however if we decide to share data in the future the data will be de-identified and your identity will not be shared.

COMPENSATION FOR INJURY
If you believe that the research procedures have resulted in an injury to you, immediately contact the Principal Investigator who is listed on the first page of this form. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care. At this time, there is no plan for any additional financial compensation. You do not, however, waive any legal rights by signing this form.

Who will know about my participation in this research study? The information that you give us will be kept confidential. In addition to members of the research team, authorized representatives of The Research Conduct and Compliance Office, University of Pittsburgh and authorized representatives of the study sponsor may look at your research records to ensure that the study is being conducted properly. Your name will not appear in any report or publication.

Is my participation in this research study voluntary? May I leave the research study if I choose to? Your participation in this research study is completely voluntary. You may leave the project at any time. Whether or not you take part in this research project or if you decide to leave the project after you have accepted to participate will not have any consequences whatsoever. All data collected up to the point of withdrawal may be used by the investigators.
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VOLUNTARY CONSENT
All of the above has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any part of this research study during the course of this study, and that such future questions will be answered by the researchers listed on the first page of this form. Any questions which I have about my rights as a research participant will be answered by the Human Subject Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212- 2668). By signing this form, I agree to participate in this research study. A copy of this consent form will be given to me. _____
_____ _____
Participant Signature Participant Printed Name Date CERTIFICATION OF INFORMED

CONSENT I certify that I have explained the nature and purpose of this research study to the above-named individual, and I have discussed the potential benefits and possible risks of study participation. Any questions the individual has about this study have been answered, and we will

always be available to address future questions as they arise.

_____ _____ _____ _____ Signature of Person Obtaining Consent Role Printed Name of Person Obtaining Consent Date

Eligibility Criteria

What is the age range of the subject population?

18 and older, all patients presenting for Mohs or Excisional Surgery with Dr. Carroll at UPMC Dermatologic Surgery
Enrolling Pitt medical students

What is their gender?

* Both males and females

Provide a justification if single gender selected:

Will any racial or ethnic subgroups be explicitly excluded from participation?

* No

For studies conducted in the U.S., do you expect that all subjects will be able to comprehend English?

* Yes

Statistical Considerations

Unpaired 2-tailed Student's t-test was used for univariate analysis of all variables for comparison of NRS means. A threshold for significance was set at $p < 0.05$. All values collected were analyzed to report mean values ± standard error from the mean.

Multivariate linear regression analysis was used to compare categorical variables (age, sex, and treatment site). Multivariate analysis of the overall cohort identified $p<0.2$ for age, sex, and treatment site. All further subgroup analysis was performed using multivariate analysis with a threshold for significance set at $p<0.05$. All statistical analyses were calculated by RK with Igor Pro (Wavemetrics, version 8) and STATA (StataCorp, version 13) software and confirmed with a consulting statistician (KMR).