Evaluating the Effectiveness of Immersive Technologies, Virtual Reality and Augmented Reality, to Increase Pain Threshold During Ice Immersion

NCT04196686
June 10, 2020

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1. PURPOSE OF THE STUDY

a. Brief Summary

b. The purpose of this study is to evaluate the effectiveness of different technologies, Virtual Reality and Augmented Reality with modifications as passive content, active content, cognitive load modulation, and positive encouragement coaching to increase the pain threshold as assessed by immersing a hand in ice water.

c. Rationale for Research in Humans

This study is designed to test the effectiveness of a virtual distraction on healthy volunteers. There is no appropriate substitute for the use of humans in this context, so humans must be used.

2. STUDY PROCEDURES

a. Procedures

1500 participants (adults, undergraduate, graduate students) recruited by research personal at a booth set up on or near the Stanford University campus. They will have the option of completing the study at the booth, or scheduling an appointment to participate at LPCH at a later time to do all the study. If interested in the study, the research staff will gauge their preferred availability to participate in the study. During the day of their scheduled study appointment, the research assistant will review the study, go over the consent forms, and answer any questions they may have about the study. Exclusion criteria includes (i) patients who do not consent (ii) are currently taking beta blockers or other chronotropic heart medication(s) (iii) have a history of severe motion sickness (iv) currently have nausea (v) currently experiencing seizures(vi) are clinically unstable (vii) have taken pain medications in the last 12 hours Inclusion criteria includes (i) greater than 18 years of age (ii)English speaking (iii) hearing intact

PHASE 1
Part 1a: 3 groups of 250 healthy volunteers will be recruited for this 2 part study. Once they consent to participate in the study, the research personnel will do a Sensory perception threshold (time, amplitude) captured via biosensors (Neurometer). Then the first group of 250 participants will be randomized into either control arm (they will not receive any kind of distraction, no technologies) or the use of Virtual Reality. The second group of 250 will be randomized into Active VR, they will play a game or Passive VR, they will be watching a movie in the VR headset. And the third group of 250 will be randomized into Augmented Reality (AR) or VR. The three groups will wait 5 minutes and each participant will switch to the opposite group (i.e. in the first group, VR group will switch to no VR group). Part 1b: Ice bath: Participants immerse hand in ice bath and starting again with their original assigned group (see attached Dahlquist et al., 2007) and keep hand submerged as long as they can withstand the cold or until 4 minutes

have elapsed, whichever comes first. Participants will not be told of the specifics of the time limit, to avoid competitiveness and expectations and will be asked for pain scores every 30 seconds.

PHASE 2
Once they consent to participate in the study, the research personnel will do a Sensory perception threshold (time, amplitude) captured via biosensors (Neurometer). Part 2a: 250 participants will be recruited and randomized into either VR or VR + Cognitive Load Modulation. Cognitive Load Modulation, increase the intensity of a game to provide more distraction; the game's audio and visuals will intensify, thereby increasing the cognitive load. Ice bath: Participants immerse hand in ice bath and starting again with their original assigned group and keep hand submerged as long as they can withstand the cold or until 4 minutes have elapsed, whichever comes first. They will be asked to inform research staff when they think they can only keep their hand immersed for 5 more seconds at which point the Cognitive Load Modulation (CLM) group will have the virtual experience intensity increased, while the controls will not. Participants will not be told of the specifics of the 4 minute time limit to avoid competitiveness and expectations. Participants will then crossover to the opposite group after a 5 minute rest period.

Part 2b:
250 participants will be recruited and randomized into either VR or VR with Positive Encouragement Coaching (PEC). One of the research assistants will be encouraging the participants to distract them. Ice bath: Participants immerse hand in ice bath and starting again with their original assigned group and keep hand submerged as long as they can withstand the cold or until 4 minutes have elapsed, whichever comes first. They will be asked to inform research staff when they think they can only keep their hand immersed for 5 more seconds at which point the PEC VR group will have the virtual experience intensity increased, while the controls will not. Participants will not be told of the specifics of the 4 minute time limit to avoid competitiveness and expectations. Participants will then crossover to the opposite group after a 5 minute rest period.

Part 2c: 250 participants will be recruited and randomized into either CLM VR or PEC VR Ice bath: Participants immerse hand in ice bath and starting again with their original assigned group and keep hand submerged as long as they can withstand the cold or until 4 minutes have elapsed, whichever comes first. They will be asked to inform research staff when they think they can only keep their hand immersed for 5 more seconds at which point the PEC VR group and the CLM VR groups will have the virtual experience intensity increased, while the VR only will not. Participants will not be told of the specifics of the 4 minute time limit to avoid competitiveness and expectations. Participants will then crossover to the opposite group after a 5 minute rest period. All the technologies: VR headset/AR headsets have been approved and meet standards established by the Hospital Instrument and Electrical Safety Committee and are currently in use in the perioperative department. All participants will have biometric sensors that will be collecting physiological metrics such as vital signs, heart rate variability, respiratory rate, etc., which will be entered into a REDCap database. The study will be conducted in LPCH and SHC facilities and clinics.

We use a calculator to determine the minimum number of subjects that need to be enrolled in a study in order to have sufficient statistical power to detect a treatment effect. For 2 independent sample study with mean of 7(SD of 1.5) in group 1, mean of 9 in group 2, alpha of 0.05, beta of 0.2 and power of 0.8, 10 patients will be required in each group. To compensate for dropouts and incomplete data, 12 patients are targeted for enrollment in each group. After enrolling the first 24 participants we ran statistics test to calculate the sample size if we want to have sufficient statistical power with the data we collected. The new sample size needs to be 250 participants in each group.

b. Procedure Risks

Using AR/VR carries minimal risk. The main risk is developing nausea and/or dizziness, which will be monitored for and can be easily treated by removing the headset. Ice bath protocols have been performed for decades and we will adhere to safety standards set by these protocols such as constant monitory of ice bath temperature via thermometer, hard time limit, rest period between phases, and heart rate monitoring via pulse oximeter.

c. Use of Deception in the Study

NA

d. Use of Audio and Video Recordings

NA

e. Alternative Procedures or Courses of Treatment

This does not involve specific treatments. No standard treatment will be withheld, the alternative to this study is for the participant not to engage in our research study.

f. Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

Yes - VR/AR technologies described here are currently in use for the entire hospital.

g. Study Endpoint(s)

The endpoint of the study will be determined by the completion of the target number of participants. The target number of participants 1500.

3. BACKGROUND

a. Past Experimental and/or Clinical Findings

While there have been previous studies that evaluate virtual distraction for decreasing pain in the medical setting, to our knowledge this will be the first to evaluate the effectiveness of several modifications including augmented reality, cognitive load modulation, and positive encouragement coaching.

[1] Tsui, B. C., Shakespeare, T. J., Leung, D. H., Tsui, J. H., & Corry, G. N. (2013). Reproducibility of current perception threshold with the Neurometer® vs the Stimpod NMS450 peripheral nerve stimulator in healthy volunteers: an observational study. Canadian Journal of Anesthesia/Journal canadien d'anesthésie, 60(8), 753-760.

[2] Dahlquist, L. M., Herbert, L. J., Weiss, K. E., & Jimeno, M. (2010). Virtual-reality distraction and cold-pressor pain tolerance: does avatar point of view matter?. Cyberpsychology, Behavior, and Social Networking, 13(5), 587-591.

[3] Dahlquist, L. M., McKenna, K. D., Jones, K. K., Dillinger, L., Weiss, K. E., & Ackerman, C. S. (2007). Active and passive distraction using a headmounted display helmet: Effects on cold pressor pain in children. Health Psychology, 26(6), 794.

[4] Forys, K. L., & Dahlquist, L. M. (2007). The influence of preferred coping style and cognitive strategy on laboratory-induced pain. Health psychology, 26(1), 22.

[5] Dahlquist, L. M., Pendley, J. S., Landtrip, D. S., Jones, C. L., & Steuber, C. P. (2002). Distraction intervention for preschoolers undergoing intramuscular injections and subcutaneous port access. Health Psychology, 21(1), 94.

[6] Gershon, J., Zimand, E., Pickering, M., Rothbaum, B. O., & Hodges, L. (2004). A pilot and feasibility study of virtual reality as a distraction for children with cancer. Journal of the American Academy of Child & Adolescent Psychiatry, 43(10), 1243- 1249.

b. Findings from Past Animal Experiments

4. DEVICES USED IN THE STUDY

a. Investigational Devices (Including Commercial Devices Used Off-Label)

Investigational Device 1	
Name:	Virtual Reality Headset-Gear VR
Description:	Portable VR headset to display a passive relaxing experience such as sitting on beach or exploring the ocean by looking around. The active experience may include playing a game to collect bananas as monkey, flying a paper airplane, or catching balls in a basket.
Significant Risk? (Y/N)	N
Rationale for Non-Significant Risk	VR headsets are commercially available devices for gaming and relaxation with insignificant risks. The possible side effects are nausea and dizziness, they can be solve with removing the headset.

5. PARTICIPANT POPULATION

a. Planned Enrollment

(i) 1500 participants will be enrolled during our study
(ii) Students, adults, visitors and personnel working or volunteering at LPCH or SHC facilities
(iii) These participants are being chosen because we are focusing on a low risk population

b. Age, Gender, and Ethnic Background

Patients 18 and older of mixed genders and ethnic backgrounds.

c. Vulnerable Populations

Up to 1500 healthy volunteers, students, adults, visitors and personnel working or volunteering at LPCH or SHC facilities could potentially be enrolled in this study. This is necessary as this study aims to investigate the effectiveness of non-invasive technologies (AR/VR/Tablet) with modifications at altering pain tolerance. . Although we expect minimal risks in this study, there may be a chance of patients experiencing intolerable symptoms such as dizziness and nausea from VR/AR use. In such case our health care providers will be notified and appropriate measures will be taken to ensure patient safety. The risk discovery of an individual's participation is mitigated by our measures to keep patients data de-identified and stored in a secure and encrypted database.

d. Rationale for Exclusion of Certain Populations

NA

e. Stanford Populations

Up to 1500 volunteers could be enrolled in the study.

f. Healthy Volunteers

NA

g. Recruitment Details

School of Medicine research assistants who are not affiliated with the volunteers in any way, will recruit via an informational booth set up on the Stanford Campus after receiving University approval and at LPCH. At the booth and at LPCH some research assistant will be running the study and other research assistants will be around to booth to inform the people about the study. The research assistants will not coerce or influence an volunteer's decision to participate. If volunteer declines interest, research personnel will respect their decision and will not pursue them for any further involvement in this study.

h. Eligibility Criteria

i. Inclusion Criteria

(i) greater than 18 years of age (ii) English speaking (iii) hearing intact

ii. Exclusion Criteria

(i) patients who do not consent
(ii) are currently taking beta blockers or other chronotropic heart medication(s)
(iii) have a history of severe motion sickness
(iv) currently
have nausea
(v) currently experiencing seizures
(vi) are clinically unstable

i. Screening Procedures

No PHI will be collected prior to enrollment. If the participant expresses interest they will be approached by a research assistant. If they decline they will not receive any further information about the study. If the participant expresses interest, the RA will proceed with the consent and appropriate stage placement, randomization will occur for the second phase (either standard of care of VR/AR/table simulation) If the potential candidate declines interest, we will respect their decision and will not pursue them for any further involvement in this study. Only authorized members of the study team will have access to patient information.

j. Participation in Multiple Protocols

Participants will be asked if they are participating or intend to enroll in other studies. Participants will be allowed to participate in more than one study if it can be determined that this poses no increased risk to the

participants or the integrity of the data collected for either study.

k. Payments to Participants

Participants will receive a $5.00 gift card for participation in this study.

l. Costs to Participants

NA

m. Planned Duration of the Study

i) Screening per patient will take approximately 10-15 minutes.
ii) Active participation for the participant will last the duration of the procedure, we estimate about 1 hour, from the time of consent to the debrief.
iii) The analysis of the data will take approximately 1-2 years.

6. RISKS

a. Potential Risks

i. Investigational devices

VR and AR headset and software- we expect a low incidence of intolerability (primarily nausea and dizziness) in less than 5% of all cases, in which case VR headset can simply be removed and any follow-up care can be assessed by the healthcare provider.

ii. Investigational drugs

NA

iii. Commercially available drugs, biologics, reagents or chemicals

NA

iv. Procedures

The VR and AR headsets unit will be placed on patients by trained staff and will have minimal risk to the patient. VR and AR headsets will be set up by trained study staff. All devices are wiped with hospital grade disinfection wipes according to hospital protocols. All devices are compliant with infection control standards at LPCH and hospital instrument and electrical compliance.

v. Radioisotopes/radiation-producing machines

NA

vi. Physical well-being

NA

vii. Psychological well-being

NA

viii. Economic well-being

NA

ix. Social well-being

NA

x. Overall evaluation of risk

NA

b. International Research Risk Procedures

NA

c. Procedures to Minimize Risk

Participants/patients will be informed that they may withdraw from the study at any time, for any reason, with no consequences for withdrawing, and the standard clinical care and procedures for their care will continue as normal. All data will be de-identified and stored in a secure, encrypted database for clinical analysis.

d. Study Conclusion

The experiment will terminate at the conclusion or enrollment. There is no anticipated interim analysis, and no reason to consider early termination based on the low level of risk associated with this study. If the patient decides that he/she does not want to participate in the study at any time, we will terminate the study.

e. Data Safety Monitoring Plan (DSMC)

i. Data and/or events subject to review

NA

ii. Person(s) responsible for Data and Safety Monitoring

NA

iii. Frequency of DSMB meetings

NA

iv. Specific triggers or stopping rules

NA

v. DSMB Reporting

NA

vi. Will the Protocol Director be the only monitoring entity? (Y/N)

NA

vii. Will a board, committee, or safety monitor be responsible for study monitoring? (Y/N)

NA

f. Risks to Special Populations

NA

7. BENEFITS

It is unknown if participants enrolled in the study will directly benefit, but we anticipate that the technology-based distractions have great potential to be used in future medical encounters.

8. PRIVACY AND CONFIDENTIALITY

All participant information and specimens are handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and privacy policies of Stanford University, Stanford Health Care, and Stanford Children's Health.