Study Protocol and Statistical Analysis Plan

Title of Study: Adjunct VR Pain Management in Acute Brain Injury

NCT Number: NCT04356963

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*Background*

The United States Department of Health and Human Services has declared a national opioid crisis as over 130 Americans die every day from an opioid overdose. Opioid use disorder usually starts with a prescription for opioids for a valid medical condition. Severe or refractory pain, as well as longer durations and higher doses of initial opioid therapies increase the risk for opioid use disorder. Patients with acute TBI may be at particular high risk for opioid use disorder. Headache is the most common complaint after TBI, present in up to 90% patients. The pain is typically severe, persistent, and refractory to medical therapies. While opioids are not recommended in headaches associated with mild TBI, data suggest that they are commonly prescribed. The long-term consequences of unabated pain and high opioid exposure in TBI patients are uncertain. Among soldiers returning from active duty who have a TBI diagnosis, nearly 60% are prescribed an opioid during the post-deployment year. We believe it is pivotal to develop novel, non-pharmacological therapeutics that effectively manage pain and reduce opioid use in the acute phase in order to mitigate risk for chronic opioid use disorder. VR has shown promise as a non-pharmacologic pain modifier. In a prior collaboration with the Colloca lab from the University of Maryland School of Nursing, we have shown that a VR environment can increase pain tolerance.

Physicians have utilized VR as a powerful distraction tool during painful procedures such as wound cleaning in burn patients, cystoscopy in urological patients, and physical therapy in orthopedic trauma patients. Hospitalized patients with persistent pain from orthopedic traumatic injuries, burns, and other complaints have benefitted from the addition of VR outside

of procedural distraction. Outpatients with chronic pain syndromes including chronic headache may also benefit. No one has previously studied the effect of VR on TBI induced headache pain.

*Aims*

Aim 1a) Assess the feasibility and explore the effects of immersive virtual reality (VR) on pain after acute traumatic injury including TBI. We will test this aim by comparing the change in numeric pain rating scale pre- and post-immersive virtual reality scenarios to the change in numeric pain rating scales pre- and post- non-immersive two-dimensional tablet-based mimics and content-less virtual reality sensory immersion.

Aim 1b) Compare effectiveness of VR therapy to non-immersive control sessions in reducing opioid use.

Aim 1c) Compare VR therapy to non-immersive control sessions on pain-related affective measures (depression and anxiety), autonomic measures (heart rate variability, pupillometry), and subjective experience measures (perceived effectiveness, anxiety). These processes have been associated with pain experience but have not been adequately explored in past virtual reality studies.

*Eligibility Criteria*

<u>Inclusion Criteria</u>

Diagnosis of Traumatic Injury (including but not limited to traumatic brain injury)

Age greater than or equal to 18 years-old

Endorsing at least moderate pain as defined by documentation of at least one numeric rating pain scale score of 3 or more in the last 24 hours.

Glasgow Coma Scale of 15

Expectd to stay in the hospital for at least twelve hours after enrollment

Exclusion Criteria

Seizure prior to enrollment

Pregnancy

non-English speaking

known intolerance of Virtual Reality

Participants should be able to consent for themselves

*Procedures*

Patients who are enrolled in the study will be identified as candidates via the PI or Sub-Investigator, or Research Coordinator. Once the patient has been identified, the research coordinator, PI, or Sub-Investigator will approach the patient and discuss the research protocol with them. If the patient agrees to participate, the study coordinator will make sure that all of the appropriate documentation (including consent) is completed before study procedures begin.

After the consent has been signed and completed, the study participant will complete a pre-study questionnaire to elicit their prior experience with the proposed therapeutic as well as several validated scales of pain, nausea, anxiety and depression, gaming addiction, suggestibility, and expectancy. They will then be given a tutorial on how to use the Virtual Reality Headset, or Head Mounted Display (HMD). The HMD that will be used for this study protocol is not limited to just the Oculus Rift or Rift S, but may also be the Samsung Odyssey Plus, and HTC Vive Pro. The research staff will go over specifics on how to use the HMD, and will remain throughout the duration of time the participant is in the virtual reality world in case they have any questions or concerns.

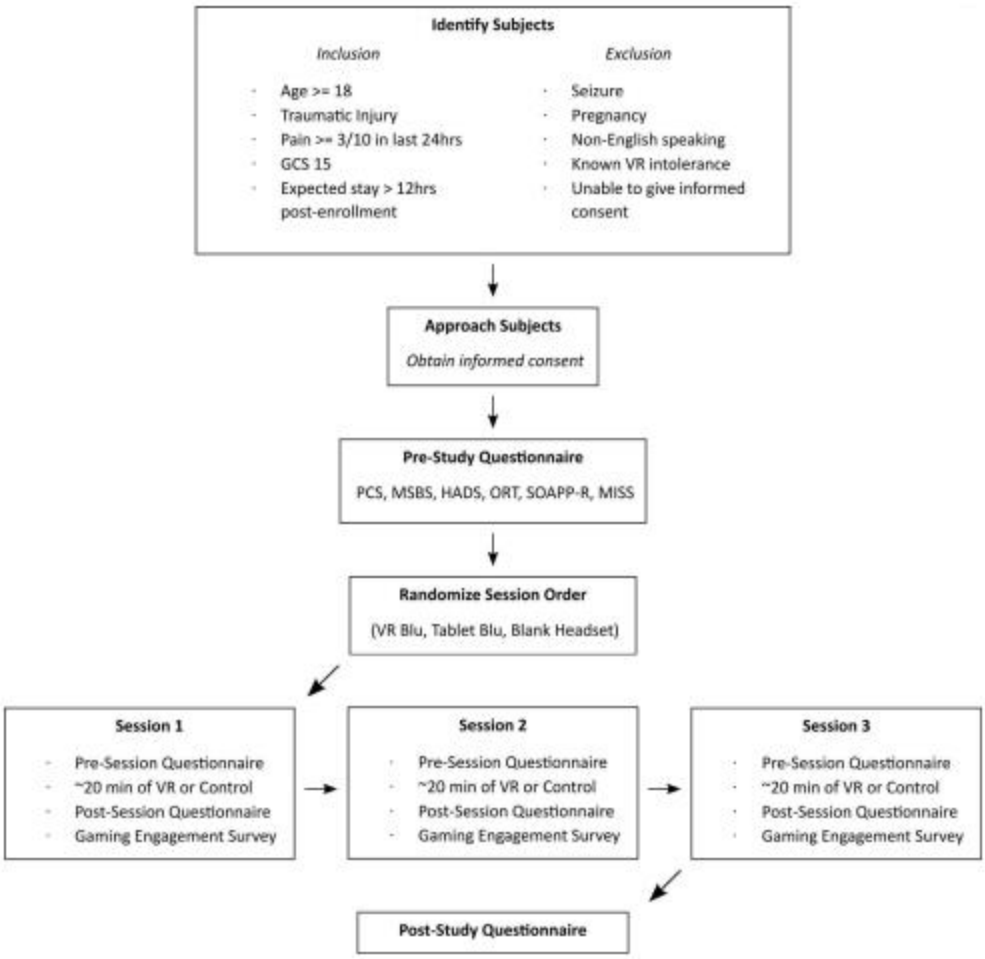
Once the participant is acquainted with the HMD, by completing their guided tutorial on how to use the headset, he or she will take part in two virtual reality sessions and two non-immersive tablet-based control sessions. One session will be meditative, where the second session will be chosen during the participants tutorial/introduction to the HMD. This environment could be a game, music, or relaxing. There will be two sessions per day including one virtual reality session and one non-immersive tablet based sessions. The virtual reality sessions and non-immersive tablet-based sessions will take place within the duration of their hospitalization. Sessions will be randomized using internet-based randomization techniques, or through mathematical programs. Participants will be allowed to complete more sessions if they desire once they complete their initial 2 VR sessions and 2 tablet-based sessions.

To be completely immersed during the sessions, the patient will also be given the option to use Noise Cancelling Headphones during the study. Some HMD headsets come with headphones attached, and some do not. The Noise Cancelling Headphones will be used with the HMD's

without headphones attached, as well as with the tablet. This will block out hospital noises, and all other forms of communication so that they can be completely immersed in their environment. If the patient needs to communicate with the Research Coordinator or any clinical team member who is at the bedside, they will be instructed to remove the Noise Cancelling headphones so that they can voice their questions or concerns.

Before and after each session, participants will answer simple questions via questionnaire (included later in this application). The patient's heart rate, blood pressure, respiratory rate, and pupil size and reactivity will be recorded before and after each session to monitor response. Opioid usage and continuous heart rate will also be collected after each VR session. This is not just limited to the scheduled VR sessions - opioid usage and continuous HR can be taken at other non-scheduled VR sessions. This will vary on a patient-to-patient basis - being that some patients may want to participate more with VR after their 2 VR:2 tablet scheduled sessions, and some may not. Pain will be assessed every 2 hours by nurses using the Numeric Rating Scale with additional assessment directly before and after each study session.
All patients will have orders for analgesia written by the treatment team. If pain is inadequately controlled, additional analgesic orders will be placed by the clinical team in communication with the research team. Should pain ratings be increased after study sessions, the nurses will notify both the clinical and research teams for assessment.

At the conclusion of all sessions, participants will complete another questionnaire to help us understand their self-perceived experience of using virtual reality.




*Sample Size Calculation*

Because participants will serve as their own control, individual variability in experiencing and reporting pain will be reduced, enhancing our ability to identify treatment effects. A sample size of 32 patients will give us 80% power to observe a 30% difference in delta pain scores (our primary outcome). As many patients will be discharged prior to being able to complete the study. We will aim for an enrollment of 60 total patients.

*Research Related Risks*

1. Loss of Confidentiality: There is a minimal risk for a loss of confidentiality when participating in a research study. However, every step to ensure the confidentiality and anonymity of results and identity will be taken. Steps will include using only an assigned code number for personally identifiable information, including contact information and name, on any documentation from this study. Moreover, electronic data will be password-protected and all paper copies of data will be stored in a locked cabinet.

2. There is a minimal risk for a breach of privacy. However, to minimize this, consent will only be obtained in private patient rooms or in a private conference room.

3. There is a risk that patients may have a difficult time using the HMD and handheld controller, which may make them frustrated or upset. At this point, the research personnel will assist them in any way they can so that the patient can use the HMD and continue on with the study protocol. The research personnel is aware that the device can be difficult to use for first time users. The PI and research personnel have developed standards of procedures on how to address this issue if it were to arise.

4. Immersion in virtual reality may cause of a sense of being in a closed environment and rarely nausea. These effects are only transitory but if you experience any discomfort, the virtual

reality headset can be removed quickly. Patients who cannot tolerate the virtual reality will prematurely end study participation.

5. Although uncommon, patients could potentially experience seizure like activity will using the HMD. Of note, the HMDs are widely available and used by the public in everyday life and require no special screening or monitoring for seizure in their use. Per the Oculus Rift product description, "Some people (about 1 in 4000) may have severe dizziness, seizures, eye or muscle twitching or blackouts triggered by light flashes or patterns, and this may occur while they are watching TV, playing video games or experiencing virtual reality, even if they have never had a seizure or blackout before or have no history of seizures or epilepsy". The PI and research personnel will ensure that patients do not suffer from seizures prior to their enrollment. During the study protocol procedures, the patient will be monitored in a hospital bed where there is extensive experience in monitoring for and treating seizures. Seizures from virtual reality headset use are known to occur in patients with photosensitive epilepsies. Traumatic brain injury is not known to produce photosensitive epilepsy. If at any time, the patient develops severe dizziness, seizures, eye or muscle twitching or blackouts triggered by light flashes or patterns the virtual reality headset will be removed and the study will be discontinued in the patient.

*Primary and Secondary Analyses*

Descriptive statistics will be used to describe the patient population. The primary outcome (Aim 1a) is the difference in change in pre- and post-session pain scores in the immersive virtual reality sessions as compared to control sessions. Secondary outcomes will include opioid usage (Aim 1b), affective measures (mood and anxiety), autonomic measures, and subjective experience measures (Aim 1c). We will use mixed effect models to analyze the differences between the ratings over time. This model allows us to run analyses utilizing all subjects despite some missing measurements (which can be expected when studying patients in an ICU setting). To investigate if demographics or patient measures of gaming addiction, suggestibility, or expectancy are related to the pain effect, we will use Pearson`s correlation between the questionnaire scores and the difference of the means of both conditions and virtual reality sessions.

*Data collection*

All source data and research documentation will be kept in a locked cabinet in the research coordinator's locked office which is in a locked office suite. Electronic data will be kept on a desktop computer which is encrypted and password-protected by the guidelines implemented from the University of Maryland School of Medicine. To ensure confidentiality, all data files will only be accessible to the research team.

*Data monitoring*

This study will be reviewed weekly by the primary investigator to assess for adverse events. An interim analysis will be conducted when 20 patients with non-TBI injuries and 20 patients with TBI have been enrolled. Safety monitoring results will be reported to the IRB.

*Device safety*

The Oculus Rift is a commercially available portable VR headset device for gaming and relaxation with nonsignificant risks. There is a precedent of using VR in hospitalised medical patients.32 46–49 In a 2018 review of 11 randomised controlled trials (including nearly 500 patients) that used VR in hospitalised patients found the VR to be feasible in the hospital and safe.46 A 2010 study evaluating VR for acute pain management after trauma did not include patients with TBI and found no safety concerns.32 Similarly, a review of 11 studies of VR for TBI rehabilitation found no safety concerns.49 We therefore believe VR to be safe in the acute phase after TBI.