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Randomized Within-Subjects Clinical Trial for Adjunctive Virtual Reality Pain Relief following Traumatic Injury

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ABSTRACT

Introduction

The annual mortality and national expense of the opioid crisis continues to rise in the United States (130 deaths/day, $50 billion/year). Opioid use disorder usually starts with the prescription of opioids for a valid medical condition. Its risk is associated with greater pain intensity and coping strategies characterized by pain catastrophizing. Non-pharmacological analgesics in the hospital setting are critical to abate the opioid epidemic. One promising intervention is virtual reality (VR) therapy. It has performed well as a distraction tool and pain modifier during medical procedures; however, little is known about VR in the acute pain setting following traumatic injury. Further, no studies have investigated VR in the setting of traumatic brain injury (TBI). This study aims to establish the safety and effect of VR therapy in the inpatient setting for acute traumatic injury, including TBI.

Methods & Analysis

In this randomized within-subjects clinical study, immersive VR therapy will be compared to two controls in patients with traumatic injury, including TBI. Affective measures such as pain catastrophizing, boredom, trait anxiety and depression will be captured prior to beginning sessions. Before and after each session we capture pain intensity and unpleasantness, additional affective measures including anxiety, as well physiological measures associated to the pain response such as heart rate and variability, pupillometry, blood pressure, and respiratory rate. The primary outcome is the change in pain intensity of the VR session compared to controls. Secondary outcomes include association of affective measures with change in VR pain intensity.

Ethics & Dissemination

The dissemination of this protocol will allow fellow researchers and funding bodies to stay abreast in their fields by providing exposure to research that may not be otherwise widely publicized. All study protocols are compliant with federal regulation and Institutional Review Board policies.

Registration

IRB# HP-00090603, Clinical Trial Registration NCT04356963

Strengths & Limitations

- Within-subjects trial design allows for a lower number of participants as each act as their own control
- Linear mixed effects modeling allows for the inclusion of subjects missing data points, a commonality in a trauma center population
- Difficulty of VR therapy administration for an inpatient acute trauma setting

INTRODUCTION

The United States Department of Health and Human Services has declared a national opioid crisis, as over 130 Americans die each day from an opioid overdose.[1,2] Additionally, non-medical use of prescription opioids has an estimated annual cost of over $50 billion to the United States economy.[3] Opioid use disorder typically starts with a prescription for opioids for a valid medical condition.[4,5] Higher doses and longer durations of opioid treatment during the acute inpatient phase of injury, increase the risk for opioid use disorder, especially when pain is severe and refractory.[4,6–8]

Patients with traumatic injuries, including acute traumatic brain injury (TBI), may be at particularly high risk for opioid use disorder. Each year in the United States an estimated 35 million people visit the ED with an injury, with nearly 2.8 million being treated for TBI.[9,10] Traumatic injury has been independently associated with persistent opioid usage.[11,12] Post-injury usage risk factors for prolonged use include pain severity and catastrophic thinking.[13,14] In TBI, the vast majority of cases are classified as mild with the most common symptom being headache, present in up to 90% of patients.[15] The pain is typically severe, persistent, and refractory to medical therapies,[16–18] with over a third of patients complaining of headache twelve months post-TBI.[19] Though opioids are not recommended in headaches associated with mild TBI,[20] data suggest that they are commonly prescribed.[17] Among soldiers returning from active duty who have a TBI diagnosis, nearly 60% are prescribed an opioid during the post-deployment year.[21,22] Limiting opioids during hospitalizations with acute pain is an important component of addressing the current opioid epidemic.[23] It is pivotal to develop novel, non-pharmacological therapeutics that effectively manage pain and reduce opioid use in the acute phase of traumatic injury to mitigate risk for chronic opioid use disorder.

Virtual reality (VR) has shown promise as a non-pharmacologic pain modifier.[24–26] Previous studies have found that hospitalized patients with persistent pain from orthopedic traumatic injuries,

burns, and other complaints have benefitted from the addition of VR.[27,28] Patients with acute brain injuries have largely been excluded from VR studies for acute pain out of concern for intolerance due to nausea and motion sickness and due to a perceived elevation in seizure risk. Thus, the safety and feasibility of VR for analgesia in patients with TBI is unknown. Moreover, a recent review of VR for other forms of acute pain revealed multiple methodological concerns in the existing literature; most studies lacked appropriate controls and focused solely on pain intensity, while neglecting other important aspects of the pain experience.[29]

We designed the current study to address these two important gaps in the literature. First, we aim to establish VR as a safe, and feasible adjunctive treatment for pain in the acute phase of traumatic injury, *including* TBI. Second, we aim to improve upon prior work by including proper control conditions in a randomized within-subjects design. We are also interested in exploring patient characteristics that may predict a more significant response to VR therapy.

Study Hypotheses

Hypothesis 1: VR therapy is a safe and feasible intervention to patients with acute traumatic injuries, including those with TBI.

Hypothesis 2: VR therapy reduces pain from traumatic injuries including TBI, while improving pain-related affective measures, autonomic measures, and subjective experience.

Hypothesis 3: Patient factors such as increased gaming engagement, boredom, suggestibility, and expectancy predict response to VR therapy.

METHODS AND ANALYSIS

Study Design

We will conduct a randomized, within-subject, crossover clinical trial, comparing the effects of an immersive VR environment against two control interventions. In one of the control interventions, identical content to the immersive VR environment will be presented in a non-immersive, tablet-based form. The other intervention will control for the external sensory deprivation of the VR system by having participants wear the VR headset without any content. We are recruiting 60 participants with traumatic injury. Participants will complete a pre-study survey to assess their baseline characteristic and symptoms, the three interventional sessions in a randomized order, and a post-study survey (Figure 1).

Patient and Public Involvement

Patients with traumatic injury and their families were not involved in setting the research question or the outcome measures, however they were involved in the selection and design of the intervention. Patients with traumatic injury provided input on which virtual reality experiences were favorable for use in the study. These patients advised that VR experiences involving calming and dynamic scenes, mild interaction, and music were more enjoyable, which guided the choice of the WEVR theBlu VR experience over other options. Patients were not involved in recruitment or conduct of the study.

Setting

The study will be conducted at the R. Adams Cowley Shock Trauma Center, a freestanding trauma hospital in Baltimore, Maryland that receives more than 7000 yearly admissions, including over 1000 patients with TBI. We started recruiting patients in October 2020 and will continue until July 2022.

Participant Recruitment

Sixty patients will be enrolled. An automated research management system will be used to screen all patients admitted to Shock Trauma. A research team member will review the medical record and determine eligibility. If the patient is a candidate for the study, they will be approached in accordance with Institutional Review Board (IRB) guidelines. The study is described in detail including the study scope, expectations of participants, potential risks and benefits, and participant rights. Patients can ask any questions they may have, and if interested in enrollment they are evaluated to assess their competency and ability to give informed consent. With adequate responses, the participants and the research team will complete the informed consent form, a Health Insurance Portability and Accountability Act (HIPAA) authorization form, and a COVID-19 statement of risk, and make copies of these for the patient, the study file, and the patient chart. Participants may withdraw from the study at any point.

Eligibility

Inclusion Criteria

Participants must (1) have a diagnosis of traumatic injury, (2) be at least 18 years of age, (3) have a Glasgow Coma Score (GCS) of 15, (4) report a numerical pain score of at least 3/10 within 24 hours of enrollment, and (5) be expected to remain hospitalized for at least 12 hours post-enrollment to complete the study protocol.

Exclusion Criteria

Excluded are participants (1) who cannot consent for themselves, (2) who have a past medical history of seizure or a known intolerance of virtual reality, (3) who are pregnant, and (4) who are non-English speaking.

Assessments

Prior to beginning the study sessions, participants will complete a survey containing questions about their prior experience with the proposed VR therapeutic, any optimism regarding the expected success of virtual reality as an analgesic, as well as several validated surveys. Surveys include: the Pain Catastrophizing Scale, the Multidimensional State Boredom Scale, the Hospital Anxiety and Depression Survey, and the Opioid Risk Tool. Participants will also complete the Multidimensional Iowa Suggestibility Scale.

The participant will be taught how to use the VR Head Mounted Display (HMD); The Oculus Rift (Oculus VR, Irvine, CA.) VR system will be used. Participants will undergo three different 20-minute sessions administered in random order and spaced a minimum of four hours apart. Immersive VR experience: theBlu (WEVR, Inc, Venice, CA.) delivered via Oculus Rift headset (Figure 2).

I) Non-immersive two-dimensional mimic: Recording of theBlu experience delivered via video on a non-immersive 2-D Asus (ASUS, Taipei, Taiwan) tablet

II) VR sensory deprivation: delivered via a blank (i.e. content-less) Oculus Rift headset

Each session will contain a pre-session survey including a numeric rating scale for their overall pain, headache pain, neck/back pain, nausea, dizziness, and light sensitivity, as well as the Spielberger State-Train Anxiety Inventory (STAI). Following the session, a post-session survey is administered which contains the same metrics, with the addition of the Brockmyer Gaming Engagement Questionnaire. Vital signs are recorded pre- and post-session, including heart rate, blood pressure, respiratory rate, and pupillometry data. Participant opioid usage throughout the duration of the study will be obtained via chart review, and continuous heart rate during each session will be collected by the research team using a pre-existing monitoring system [30]. At the conclusion of all sessions, participants will complete

another questionnaire to help us understand their self-perceived experience of using VR compared to control sessions.

All participants will have orders for analgesia written by the treatment team, independent of the research team, who are blinded to the session order. 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 both the clinical and research teams will be notified for assessment.

Outcomes Measured

The primary outcome is reduction in pain severity measured by the pre- and post-session numerical rating scale for VR sessions as compared to controls. Exploratory secondary outcomes include pain assessment per the Trauma Function and Comfort Assessment, opioid usage, affective measures (anxiety), autonomic measures (pupillary maximum constriction velocity and relative constriction amplitude, and heart rate variability), and subjective experience measures.

The State-Trait Anxiety Inventory (STAI) is an anxiety affective measure, which we suspect will improve following immersive virtual reality [31]. The Brockmyer Gaming Engagement Questionnaire is a measure of immersion, flow, absorption, and other key concepts that correspond to how people experience games, which we hypothesize may correlate with a participant's pain reduction response [32]. Pre-study responses to the Hospital Anxiety and Depression Scale, Pain Catastrophizing Scale, and Multidimensional Iowa Suggestibility Scale (MISS) will be tested for any correlation to pain response. The Hospital Anxiety and Depression Scale is a measure of anxiety or depressive states that is stable across age groups and demographics[33]. The MISS is a measure of susceptibility, defined by an individual's tendency to accept extrinsic messages [34].

Sample Size Calculation

Prior work suggests that a 33% pain intensity difference or a 2-point difference on a 0-10 pain numeric rating scale are appropriate surrogates for a patient-determined clinically important response.[35] We will enroll 60 patients, projecting a study dropout of 30%, leaving us with 42 patients to give us an 80% likelihood to detect a treatment difference at a once-sided .05 significance level.[36,37]

Data Analysis

Descriptive statistics will be used to characterize the patient population. Mixed effect models will be used to analyze the differences between the ratings over time to allow for missing data expected in a trauma population.[38] To investigate if demographics or patient measures of anxiety/depression, boredom, or suggestibility are related to the pain effect, we will use Pearson`s correlation between the questionnaire scores and the difference of the means of pain reduction measures for all sessions. Analysis will be performed using the IBM Statistical Package for Social Sciences (SPSS v.24) software.

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.

Ethics and Dissemination

The dissemination of this protocol will allow fellow researchers and funding bodies to stay up to date in their fields by providing exposure to research that may not be otherwise widely publicized.

All study protocols are compliant with federal regulation and the University of Maryland Baltimore's Human Research Protections and Institutional Review Board (IRB) policies. The protocol is IRB approved and active (protocol number HP-00090603) and registered on ClinicalTrials.gov (registration number NCT04356963).

Study involvement will be voluntary, and participants may withdraw at any time. All study drop-outs or withdrawals will be documented. Any adverse effects from the study intervention will be documented and reported, and the study will be ceased with that individual.

Device Safety

The Oculus Rift is a commercially available portable virtual reality headset device for gaming and relaxation with nonsignificant risks. There is a precedent of using virtual reality in hospitalized medical patients [27,39–42]. In a 2018 review of 11 randomized controlled trials (including nearly 500 patients) that used virtual reality in hospitalized patients found VR to be feasible in the hospital and safe.[39] A 2010 study evaluating VR for acute pain management after trauma did not include patients with TBI and found no safety concerns.[27] Similarly, a review of 11 studies of VR for TBI rehabilitation found no safety concerns.[42] We therefore believe VR to be safe in the acute phase after TBI.

Figure Legends/Captions

Figure 1. Study flow sheet.

Figure 2. Study participant performing VR therapy session.

Author Contributions

RF drafted the manuscript and revised it critically for important intellectual content. AR, MK, YW, LC revised the manuscript critically for important intellectual content. SBM and NAM designed the work and revised the manuscript critically for important intellectual content.

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Competing Interests Statement

Dr. Morris reports no conflicts. Dr. Murthi reports no conflicts. Dr. Colloca reports no conflicts.

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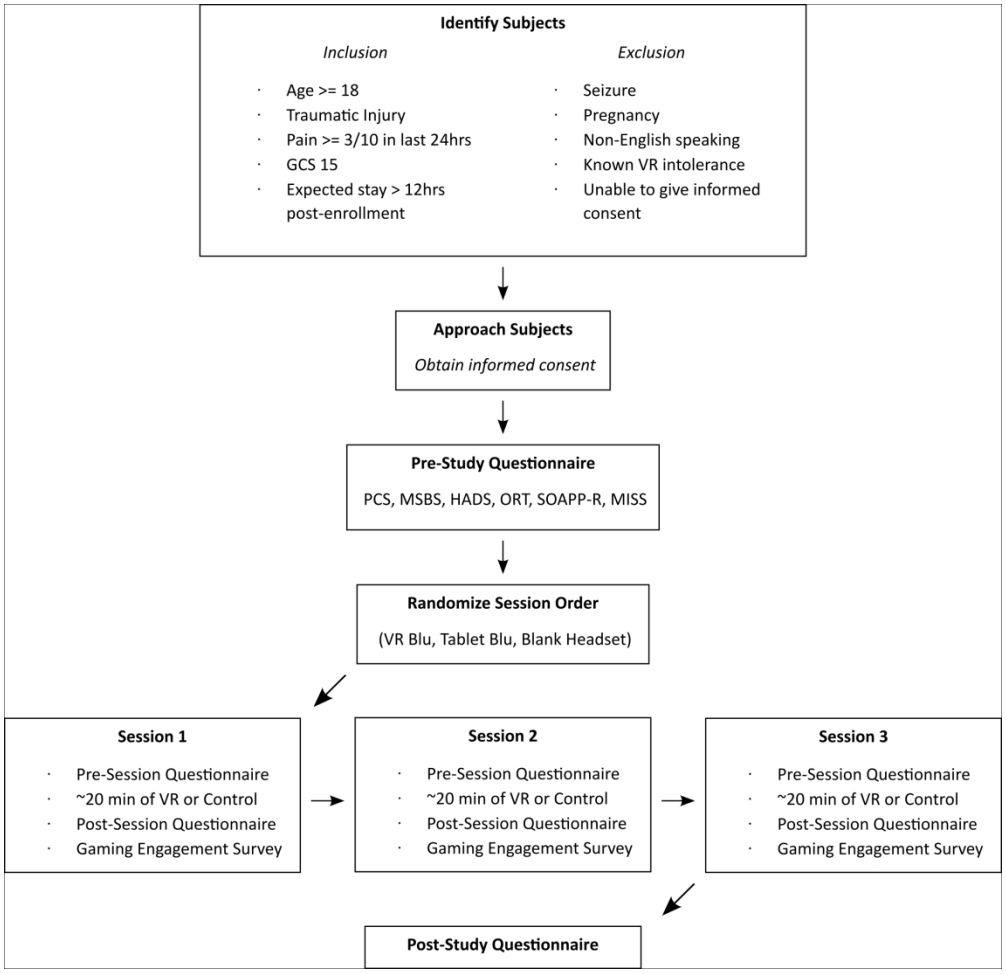

Figure 1. Study flow sheet.

501x484mm (118 x 118 DPI)

Figure 2. Study participant performing VR therapy session.

1400x731mm (72 x 72 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1-2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7-8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	9
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	N/A
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5, 7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	8 – 9
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8 – 9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8 – 9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11
	13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	N/A
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	N/A
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	8
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	N/A
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	N/A
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	N/A
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	16

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Protocol for a Randomized Within-Subjects Clinical Trial for Adjunctive Virtual Reality Pain Relief following Traumatic Injury

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Protocol for a Randomized Within-Subjects Clinical Trial for Adjunctive Virtual Reality Pain Relief following Traumatic Injury

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ABSTRACT

Introduction

The annual mortality and national expense of the opioid crisis continues to rise in the United States (130 deaths/day, $50 billion/year). Opioid use disorder usually starts with the prescription of opioids for a medical condition. Its risk is associated with greater pain intensity and coping strategies characterized by pain catastrophizing. Non-pharmacological analgesics in the hospital setting are critical to abate the opioid epidemic. One promising intervention is virtual reality (VR) therapy. It has performed well as a distraction tool and pain modifier during medical procedures; however, little is known about VR in the acute pain setting following traumatic injury. Further, no studies have investigated VR in the setting of traumatic brain injury (TBI). This study aims to establish the safety and effect of VR therapy in the inpatient setting for acute traumatic injuries, including TBI.

Methods & Analysis

In this randomized within-subjects clinical study, immersive VR therapy will be compared to two controls in patients with traumatic injury, including TBI. Affective measures including pain catastrophizing, trait anxiety and depression will be captured prior to beginning sessions. Before and after each session we capture pain intensity and unpleasantness, additional affective measures, and physiological measures associated with pain response such as heart rate and variability, pupillometry, and respiratory rate. The primary outcome is the change in pain intensity of the VR session compared to controls.

Ethics & Dissemination

Dissemination of this protocol will allow researchers and funding bodies to stay abreast in their fields through exposure to research not otherwise widely publicized. Study protocols are compliant with federal regulation and University of Maryland Baltimore's Human Research Protections and Institutional Review Board. Study results will be published upon completion of enrollment and analysis, and de-identified data can be shared by request to the corresponding author.

Registration

IRB# HP-00090603, Clinical Trial# NCT04356963

Strengths & Limitations

- Within-subjects trial design allows for a lower number of participants as each act as their own control
- Linear mixed effects modeling allows for the inclusion of subjects missing data points, a commonality in a trauma center population
- Difficulty of VR therapy administration for an inpatient acute trauma setting

INTRODUCTION

The United States Department of Health and Human Services has declared a national opioid crisis, as over 130 Americans die each day from an opioid overdose.[1,2] Additionally, non-medical use of prescription opioids has an estimated annual cost of over $50 billion to the United States economy.[3] Opioid use disorder typically starts with a prescription for opioids for a medical condition.[4,5] Higher doses and longer durations of opioid treatment during the acute inpatient phase of injury, increase the risk for opioid use disorder, especially when pain is severe and refractory.[4,6–8]

Patients with traumatic injuries, including acute traumatic brain injury (TBI), may be at particularly high risk for opioid use disorder. Each year in the United States an estimated 35 million people visit the ED with an injury, with nearly 2.8 million being treated for TBI.[9,10] Traumatic injury has been independently associated with persistent opioid usage, with one study indicating a 73% increase in likelihood of reporting persistent opioid usage.[11,12] Post-injury usage risk factors for prolonged use include pain severity, catastrophic thinking, and depression.[11,13,14] Patients suffering depressive symptoms may be up to three times as likely to report persistent opioid usage post-traumatic injury.[11] In TBI, the vast majority of cases are classified as mild with the most common symptom being headache, present in up to 90% of patients.[15] The pain is typically severe, persistent, and refractory to medical therapies,[16–18] with over a third of patients complaining of headache twelve months post-TBI.[19] Though opioids are not recommended in headaches associated with mild TBI,[20] data suggest that they are commonly prescribed.[17] Among soldiers returning from active duty who have a TBI diagnosis, nearly 60% are prescribed an opioid during the post-deployment year.[21,22] In study of patients with acute neurological injury suffering from aneurysmal subarachnoid hemorrhage, opioid use was associated with discrete pain trajectories, pain burden, and craniotomy.[23,24] Opioid sparing during hospitalizations with acute pain is an important component of addressing the current opioid epidemic.[25] It is pivotal to develop novel, non-pharmacological therapeutics that effectively manage

pain and reduce opioid use in the acute phase of traumatic injury to mitigate risk for chronic opioid use disorder.

Virtual reality (VR) has shown promise as a non-pharmacologic pain intervention and adjunctive pain-reduction therapy.[26–29] It has been suggested that VR may serve as a pain therapeutic capable of reducing the incidence of prescription opiate usage, however, this has not yet been determined.[30,31] Previous studies have found that hospitalized patients with persistent pain from orthopedic traumatic injuries, burns, and other complaints have benefitted from the addition of VR to standard of care treatments.[32,33] Patients with acute brain injuries have largely been excluded from VR studies for acute pain out of concern for intolerance due to nausea and motion sickness and due to a perceived elevation in seizure risk. Thus, the safety and feasibility of VR for analgesia in patients with TBI is unknown. Moreover, a recent review of VR for other forms of acute pain revealed multiple methodological concerns in the existing literature; most studies lacked appropriate controls and focused solely on pain intensity, while neglecting other important aspects of the pain experience.[34]

We designed the current study to address these two important gaps in the literature. First, we aim to establish VR as a safe, and feasible adjunctive treatment for pain in the acute phase of traumatic injury, *including* TBI. Second, we aim to improve upon prior work by including proper control conditions in a randomized within-subjects design. We are also interested in exploring patient characteristics that may predict a more significant response to VR therapy.

Study Hypotheses

Hypothesis 1: VR therapy is a safe and feasible intervention for patients with acute traumatic injuries, including those with TBI.

Hypothesis 2: VR therapy reduces pain from traumatic injuries including TBI, while improving pain-related affective measures, autonomic measures, and subjective experience.

Hypothesis 3: Patient factors such as increased gaming engagement, boredom, suggestibility, and expectancy predict response to VR therapy.

METHODS AND ANALYSIS

Study Design

We will conduct a randomized, within-subject, crossover clinical trial, comparing the effects of an immersive VR environment against two control interventions. In one of the control interventions, identical content to the immersive VR environment will be presented in a non-immersive, tablet-based form. The other intervention will control for the external sensory deprivation of the VR system by having participants wear the VR headset without any content. We are recruiting 60 participants with traumatic injury. Participants will complete a pre-study survey to assess their baseline characteristic and symptoms, the three interventional sessions in a randomized order, and a post-study survey (Figure 1).

Patient and Public Involvement

Patients with traumatic injury and their families were not involved in setting the research question or the outcome measures, however they were involved in the selection and design of the intervention. Patients with traumatic injury provided input on which virtual reality experiences were favorable for use in the study. These patients advised that VR experiences involving calming and dynamic scenes, mild interaction, and music were more enjoyable, which guided the choice of the WEVR theBlu VR experience over other options. Patients were not involved in recruitment or conduct of the study.

Setting

The study will be conducted at the R. Adams Cowley Shock Trauma Center, a freestanding trauma hospital in Baltimore, Maryland that receives more than 7000 yearly admissions, including over 1000 patients with TBI. We started recruiting patients in October 2020 and will continue until July 2022.

Participant Recruitment

Sixty patients will be enrolled. An automated research management system will be used to screen all patients admitted to Shock Trauma. A research team member will review the medical record and determine eligibility. If the patient is a candidate for the study, they will be approached in accordance with Institutional Review Board (IRB) guidelines. The study is described in detail including the study scope, expectations of participants, potential risks and benefits, and participant rights. Additionally, at this time it is determined if the location of the patient injury would preclude the use of the VR headset. Patients can ask any questions they may have, and if interested in enrollment they are evaluated to assess their competency and ability to give informed consent. With adequate responses, the participants and the research team will complete the informed consent form, a Health Insurance Portability and Accountability Act (HIPAA) authorization form, and a COVID-19 statement of risk, and make copies of these for the patient, the study file, and the patient chart. Participants may withdraw from the study at any point.

Eligibility

Inclusion Criteria

Participants must (1) have a diagnosis of traumatic injury, (2) be at least 18 years of age, (3) have a Glasgow Coma Score (GCS) of 15, (4) report a numerical pain score of at least 3/10 within 24 hours of enrollment, and (5) be expected to remain hospitalized for at least 12 hours post-enrollment to complete the study protocol.

Exclusion Criteria

Excluded are participants (1) who cannot consent for themselves, (2) who have a past medical history of seizure or a known intolerance of virtual reality, (3) who are pregnant, and (4) who are non-English

speaking. 'Known inability to use virtual reality' has typically presented itself as patients self-reporting dizziness after their previous VR experiences. Although the study has not yet encountered it to date, any report of past acute stress disorder or seizure secondary to immersive VR would also be excluded.

Assessments

Prior to beginning the study sessions, participants will complete a survey containing questions about their prior experience with the proposed VR therapeutic, any optimism regarding the expected success of virtual reality as an analgesic, as well as several validated surveys. Surveys include: the Pain Catastrophizing Scale, the Multidimensional State Boredom Scale, the Hospital Anxiety and Depression Survey, and the Opioid Risk Tool. Participants will also complete the Multidimensional Iowa Suggestibility Scale.

The participant will be taught how to use the VR Head Mounted Display (HMD); The Oculus Rift (Oculus VR, Irvine, CA.) VR system will be used. Participants will undergo three different 20-minute sessions administered in random order and spaced a minimum of four hours apart. Immersive VR experience: theBlu (WEVR, Inc, Venice, CA.) delivered via Oculus Rift headset (Figure 2). This immersive experience simulates the participant observing naturally relaxing and dynamic environment of a coral reef and has been utilized in other studies to induce relaxation and precepted presence.[35,36]

I) Non-immersive two-dimensional mimic: Recording of theBlu experience delivered via video on a non-immersive 2-D Asus (ASUS, Taipei, Taiwan) tablet

II) VR sensory deprivation: delivered via a blank (i.e. content-less) Oculus Rift headset

Each session will contain a pre-session survey including a numeric rating scale for their overall pain, headache pain, neck/back pain, nausea, dizziness, and light sensitivity, as well as the Spielberger State-Train Anxiety Inventory (STAI). Following the session, a post-session survey is administered which contains the same metrics, with the addition of the Brockmyer Gaming Engagement Questionnaire.

Vital signs are recorded pre- and post-session, including heart rate, blood pressure, respiratory rate, and pupillometry data. Participant chronic pain history and pre-hospital opioid usage as well as in-hospital opioid usage and pain scores throughout the duration of the study will be obtained via chart review, and continuous heart rate during each session will be collected by the research team using a pre-existing monitoring system [32]. At the conclusion of all sessions, participants will complete another questionnaire to help us understand their self-perceived experience of using VR compared to control sessions.

A team member will be present during all sessions. If the participant appears distressed or requests to have the headset removed this will be done immediately and the negative reaction recorded. All participants will have orders for analgesia written by the treatment team, independent of the research team, who are blinded to the session order. 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 both the clinical and research teams will be notified for assessment. Medication effects such as receiving pain therapeutics immediately prior to a session is partially mitigated by the study randomized within-subject design, as the incidence of pain therapeutics should remain uniform across the immersive VR and control conditions. Additionally, participant opioid dosage and times are recorded and coincidence with study procedures will be controlled for during data analysis.

Outcomes Measured

The primary outcome is reduction in pain severity measured by the pre- and post-session numerical rating scale for VR sessions as compared to controls. Exploratory secondary outcomes include pain assessment per the Trauma Function and Comfort Assessment, opioid usage, pain durability post-

session, affective measures (anxiety), autonomic measures (pupillary maximum constriction velocity and relative constriction amplitude, and heart rate variability), and subjective experience measures.

The State-Trait Anxiety Inventory (STAI) is an anxiety affective measure, which we suspect will improve following immersive virtual reality [33]. The Brockmyer Gaming Engagement Questionnaire is a measure of immersion, flow, absorption, and other key concepts that correspond to how people experience games, which we hypothesize may correlate with a participant's pain reduction response [34]. Pre-study responses to the Hospital Anxiety and Depression Scale, Pain Catastrophizing Scale, and Multidimensional Iowa Suggestibility Scale (MISS) will be tested for any correlation to pain response. The Hospital Anxiety and Depression Scale is a measure of anxiety or depressive states that is stable across age groups and demographics[35]. The MISS is a measure of susceptibility, defined by an individual's tendency to accept extrinsic messages [36].

The safety and feasibility of immersive VR for patients with acute injury or traumatic brain injury will be qualified in several ways. The typical medical concerns for immersive VR are seizures and motion sickness. During and after each session, the research team monitors patients for seizure. Any patients experiencing seizure will have the treatment team notified, will have their study participation end, and a record of the adverse event will be made for the analysis of study safety. Additionally, before and after each session patients report their dizziness and nausea levels, as well as affective measures of stress through the STAI described above. The incidence of seizure, increased dizziness or nausea, or patients being unable to tolerate sessions is recorded and utilized to characterize the safety and feasibility of the study in an in-patient acute trauma setting.

Sample Size Calculation

Prior work suggests that a 33% pain intensity difference or a 2-point difference on a 0-10 pain numeric rating scale are appropriate surrogates for a patient-determined clinically important response.[37] We

will enroll 60 patients, projecting a study dropout of 30%, leaving us with 42 patients to give us an 80% likelihood to detect a treatment difference at a one-sided .05 significance level.[38,39]

Data Analysis

Descriptive statistics will be used to characterize the patient population. Mixed effect models will be used to analyze the differences between the ratings over time to allow for missing data expected in a trauma population.[40] To investigate if demographics or patient measures of anxiety/depression, boredom, or suggestibility are related to the pain effect, we will use Pearson`s correlation between the questionnaire scores and the difference of the means of pain reduction measures for all sessions. Analysis will be performed using the IBM Statistical Package for Social Sciences (SPSS v.24) software.

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.

Ethics and Dissemination

The dissemination of this protocol will allow fellow researchers and funding bodies to stay up to date in their fields by providing exposure to research that may not be otherwise widely publicized.

All study protocols are compliant with federal regulation and the University of Maryland Baltimore's Human Research Protections and Institutional Review Board (IRB) policies. The protocol is IRB approved and active (protocol number HP-00090603 version 9 valid until July 19th, 2022) and registered on ClinicalTrials.gov (registration number NCT04356963). All past and future modifications to the protocol undergo IRB approval prior to implementation by the research team.

Study involvement will be voluntary, and participants may withdraw at any time. All study drop-outs or withdrawals will be documented. Any adverse effects from the study intervention will be documented and reported, and the study will be ceased with that individual.

Device Safety

The Oculus Rift is a commercially available portable virtual reality headset device for gaming and relaxation with nonsignificant risks. There is a precedent of using virtual reality in hospitalized medical patients [27,41–44]. In a 2018 review of 11 randomized controlled trials (including nearly 500 patients) that used virtual reality in hospitalized patients found VR to be feasible in the hospital and safe.[41] 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.[44] We therefore believe VR to be safe in the acute phase after TBI.

Figure Legends/Captions

Figure 1. Study flow sheet.

Figure 2. Study participant performing VR therapy session.

Author Contributions

RF drafted the manuscript and revised it critically for important intellectual content. AR, MK, YW, LC revised the manuscript critically for important intellectual content. SBM and NAM designed the work and revised the manuscript critically for important intellectual content.

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Competing Interests Statement

None declared.

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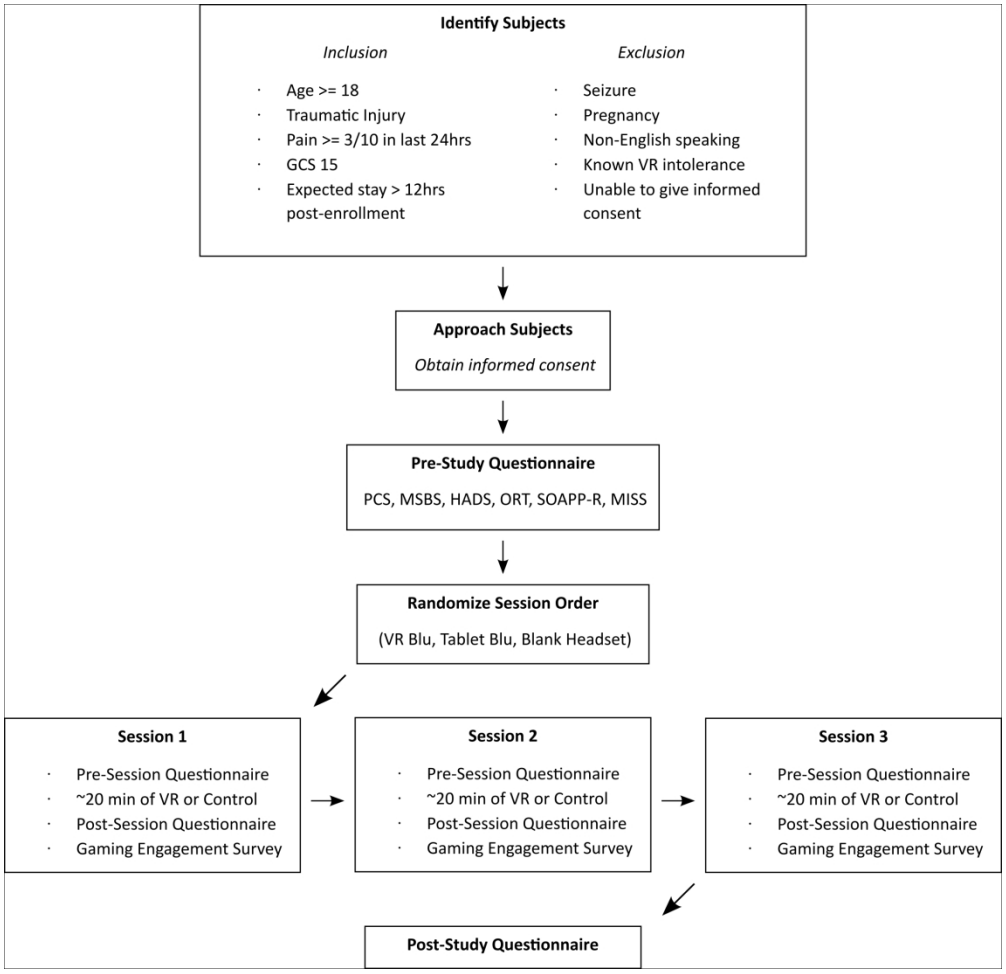

Figure 1. Study flow sheet.

501x484mm (118 x 118 DPI)

Figure 2. Study participant performing VR therapy session.

1400x731mm (72 x 72 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Page #	Section/item	Item #	Description
	Administrative information		
1	Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
2	Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
		2b	All items from the World Health Organization Trial Registration Data Set
10	Protocol version	3	Date and version identifier
11	Funding	4	Sources and types of financial, material, and other support
11	Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
		5b	Name and contact information for the trial sponsor
		5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
		5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
	Introduction		
3	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
		6b	Explanation for choice of comparators
4	Objectives	7	Specific objectives or hypotheses
5	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

	Methods: Participants, interventions, and outcomes		
5	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
6	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
7	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
8	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
5-7	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
9	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
6	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
	Methods: Assignment of interventions (for controlled trials)		
	Allocation:		
7	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

7-8	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
8	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
	Methods: Data collection, management, and analysis		
7-8	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
n/a		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
9	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
9	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
	Methods: Monitoring		
9	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
9,10	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
9	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
	Ethics and dissemination		
n/a	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
10	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
6	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
9	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
11	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
1	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
n/a	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
2, 10	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
		31b	Authorship eligibility guidelines and any intended use of professional writers
		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

	Appendices		
Supplement	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
n/a	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.