Virtual Reality for Improving Pain and Distress in Patients with Advanced Stage Colorectal Cancer (VR Blue)

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Purpose of the Study

Aim 1: Examine the feasibility, acceptability and safety of a 30-minute VR Blue session in patients with advanced colorectal cancer.

Hypothesis: Feasibility will be determined by accrual (N=20 patients over 6 months), >80% adherence to the protocol (defined as the degree to which participants are willing and able to complete the 30-minute VR exposure), and >80% completed data (measured by percent data collected at the study appointment, including pre-, midpoint, and post-VR assessments). Acceptability will be demonstrated by 80% of participants reporting VR satisfaction on the Client Satisfaction Questionnaire (mean score of 7/8). Safety of the VR protocol will be demonstrated by 80% of participants completing the VR session without significant side effects, such as motion sickness, dizziness, headache, and nausea.

Aim 2: Collect initial data on the impact of VR Blue on pain, tension and distress, and describe the relationship between pre- to post-VR changes in cognitive variables (i.e., pain catastrophizing, pain self-efficacy) and changes in pain, tension and distress over the course of the VR session.

Hypothesis: 2A. Reductions in pain, tension and distress will be demonstrated during the VR session in colorectal cancer patients. 2B. Pre- to post-VR reductions in pain catastrophizing and increases in pain self-efficacy will be correlated with improvements in pain, tension and distress occurring over the course of the VR session.

Aim 3: Gather qualitative post-session data on patients' experiences, thoughts and feelings about VR to optimize VR Blue for a future randomized clinical trial testing a multi-session VR protocol.

Hypothesis: This data will lead to optimization and manualization of a multi-session VR Blue protocol to manage pain in advanced colorectal cancer patients that can be tested in a larger, randomized clinical trial.

Background & Significance

Colorectal cancer is one of the most common cancers with an estimated nearly 150,000 new cases diagnosed in 2019 and over 50,000 deaths across the United States.1 It is the fourth most commonly diagnosed malignancy and the second leading cause of cancer mortality.1,2Advanced stage (stage IV) cancers are associated with the highest cancer mortality and morbidity rates for adults in the United States;3advanced colorectal cancer causes over half a million deaths every year.4

Many advanced colorectal cancer patients report high levels of pain and psychological distress to be especially burdensome consequences of cancer.5-10These symptoms are persistent and debilitating for patients, and negatively impact overall quality of life.5,11-13 Despite their prevalence, these symptoms often are not adequately treated in advanced cancer patients. Traditional analgesic and other medication regimens for pain and symptom management often do not fully relieve symptoms and cancer patients report significant side effects (e.g., constipation, nausea, sedation) that limit their use of these medications.14,15Non-pharmacological pain management strategies are needed to treat pain and

pain-related symptoms in advanced stage cancer patients. VR could represent a valuable addition to our current armamentarium of treatments for persistent pain in palliative care patients.

Recent evidence suggests Virtual Reality (VR) interventions can lead to reductions in pain for patients with acute pain conditions.16-21VR has not been widely tested in patients with persistent pain, though VR provides individuals with an immersive computer-generated environment that can reduce persistent pain and pain-related tension and distress.18 Due to their late-stage disease and persistent pain, many advanced colorectal cancer patients report negative pain-related cognitions (e.g., pain catastrophizing) and low confidence that they can control pain (e.g., self-efficacy for pain management). VR may be particularly useful for advanced colorectal cancer patients having persistent pain in that it can impact cognitive pathways by decreasing pain catastrophizing and increasing pain self-efficacy to improve pain control and moderate pain signaling.16These cognitive pathways have been shown to be important for pain reduction within the context of cognitive-behavioral pain management protocols.

Our group (Drs. Keefe and Somers) has a long track record of developing novel cognitive-behavioral treatment protocols for managing persistent disease-related pain (e.g., pain due to cancer and arthritis).22-30 Our experience in moving treatment protocols from the pilot trial phase to rigorous efficacy and effectiveness trials and into clinical practice enhances the likelihood that the proposed study will successfully lead to a program of VR research in advanced cancer patients. The involvement of Dr. Colloca (an internationally recognized pain researcher and study consultant) who has conducted research on VR Blue in healthy volunteers and provided input into the design of this study further enhances the likelihood that useful findings will emerge from the proposed study.

The objective of this pilot work is to gather initial data on advanced colorectal cancer patients' immediate response to a single VR session. This preliminary data will be used to optimize VR Blue for future study testing the efficacy of a multi-session VR protocol for managing pain in advanced colorectal patients.

Design & Procedures

Overview of Study Design. We will examine the feasibility, acceptability, safety, and impact of exposing patients to a single 30-minute virtual underwater/sea environment (VR Blue) for reducing pain and pain-related symptoms in patients with advanced stage colorectal cancer.

Selection of Subjects. Participants will include 20 adult colorectal cancer patients with advanced stage disease recruited from the gastrointestinal oncology clinic at the Duke Cancer Institute and from Duke Regional. Eligibility criteria include: a) age 21-85, b) stage IV cancer diagnosis, c) moderate clinical pain documented in medical chart (>4 on 0-10 scale) and confirmed on the day of their study appointment (>4/10), d) ability to read and speak English, e) self-reported normal or corrected to normal vision, and f) self-reported normal hearing. Patients will be excluded if they have: a) a serious mental illness (e.g., schizophrenia, bipolar disorder), b) a medical condition that contraindicates safe participation (e.g., recent myocardial infarction), or c) visual, hearing, or cognitive impairment that will interfere with their ability to engage in VR. Patients will NOT be excluded if they report pain under <4/10 on the day of the study appointment. If they have already arrived to their in person session and do not report pain at a

>4/10, they will not be considered ineligible or turned away; we will still move them through the VR Blue intervention protocol if they are otherwise eligible.

Recruitment. Participants in this study (N=20) will be patients with stage IV colorectal cancer recruited from the Duke Cancer Center in Durham, NC and the Duke Regional Hospital in Durham, NC. Oncology physician champion and gastrointestinal medical oncology clinical lead, Hope Uronis, MD, MHS (see letter of support) will assist with recruitment. Potential participants will be identified based on a stage IV cancer diagnosis. To assess eligibility, basic patient information will be gathered through the use of electronic medical records (i.e., DSR/DEDUCE) under a Waiver of Consent and HIPAA authorization. In accordance to the Duke guidelines, study staff will contact patients to discuss their interest in the study without first approaching their physician for approval. Potential participants will be asked: a) About their pain with the questions, “Have you had pain on most days of the month for the past 3 months?" and, asked on the day of the scheduled study appointment (Procedures), “Do you have pain today at a 4 or greater on a scale from 0-10?” They must answer “yes” to both questions to be eligible; b) A 6-item Mini-Mental State Exam (“Orientation” and “Registration” subscales). If the participant gets more than 2 items wrong they will be excluded; and c) About their vision and hearing. They will be asked “Do you have moderate or severe problems reading text on a page or computer screen even when you are wearing reading glasses?” and “Do you have moderate or severe problems with your hearing even when you are using a hearing aid?” They must answer “No” to both questions to be eligible. Patients who meet this eligibility criteria and express interest in the study will be recruited and scheduled for a study appointment at the study team’s lab (Procedures).

Procedures. Study Appointment. The study appointment will take place at the Duke Pain Prevention and Treatment Research Program office. At this appointment, research staff will explain study procedures and conduct informed consent. Once informed consent is obtained, patients (N=20) will complete the pre-VR assessment (<30 min) via REDCap, a HIPAA/PDPA compliant, web-based survey system. Following completion of this assessment, participants will complete the VR exposure and the midpoint assessment. Participants will then complete the post-VR assessment immediately following VR Blue exposure. Participants will be compensated $40 for completing this study appointment. Participants will continue to receive usual care and will not be asked to change or decline any strategies for pain management.

Virtual Reality Exposure. We will gather preliminary data on participants’ response to a single 30-minute laboratory-based virtual reality underwater/sea environment (VR Blue) session. VR Blue is an immersive computer-generated environment featuring calming scenic graphics and relaxing nature music. VR Blue has been shown to increase tolerance for thermal pain stimuli in healthy participants by Dr. Colloca, consultant on this application. In the proposed study, a member of the study team will familiarize the participant with the VR glasses and screen, and guide them through a demonstration of the VR environment. Participants will be oriented to the VR’s video and auditory stimuli with an emphasis on becoming relaxed and fully immersed in the virtual environment. Participants will be instructed to pay close attention to the virtual environment around them to cultivate their awareness of what they see. Following this orientation, the participant will complete the 30-minute VR exposure. At the midpoint, participants will be asked to provide ratings of pain, tension and distress.

Study Measures. Aim 1: Feasibility will be assessed by examining (a) study accrual (N=20 over 6 months), (b) protocol adherence (>80% adherence to the protocol [defined in this study as the degree to which participants are willing and able to complete the 30-minute VR exposure]), and (c) completed data (>80% data collected at the study appointment, including pre-, midpoint, and post-VR assessments). Acceptability will be assessed post-VR using the Client Satisfaction Questionnaire.31 Safety of the VR protocol will be assessed based on participants' report of VR side effects, such as motion sickness, dizziness, headache, nausea, or other negative physical reactions. Aim 2: Pre-, midpoint- and post-session ratings of pain, tension, stress, anxiety, and mood. Pain. Pain will be assessed using the Brief Pain Inventory (BPI) measuring pain severity and interference. This measure has been widely used in cancer patients. Tension, Stress, Anxiety and Mood. Tension, stress, anxiety and mood will be measured with Visual Analogue Scale (VAS) items with ratings ranging from 0 to 100. The timeframe reference will be "right now". VAS's for measuring tension, stress, anxiety and mood have been used in prior VR studies. Pre- and post-session measures of expectancy and enjoyment. We will use Visual Analogue Scale (VAS) items with ratings ranging from 0 to 100 to measure how much participants expect to improve from participating in the VR Blue intervention (pre) and how much they enjoyed participating in the VR Blue intervention (post). Pre- and post-session measures of pain catastrophizing and self-efficacy for pain. Pain Catastrophizing. Pain catastrophizing will be measured with the Coping Strategies Questionnaire's Pain Catastrophizing subscale. The timeframe reference will be "right now". Items will be rated on a scale ranging from 0=never do to 6=always do when in pain. Pain Self-Efficacy. Self-efficacy will be measured using items adapted from the self-efficacy for pain management subscale of the Chronic Pain Self-Efficacy Scale. For example, participants will be asked, "How confident are you that you could use virtual reality to decrease your pain?" Items are rated on a 10-point scale ranging from 10=very uncertain to 100=very certain. Scores are averaged to give an overall value for pain self-efficacy. Aim 3: We will conduct exit interviews with participants to collect qualitative data to refine and improve the VR protocol.

Data Analysis and Statistical Considerations. Analyses for Aim 1. Feasibility will be assessed by examining accrual, adherence and data completion. Accrual will be indicated by meeting the recruitment goal of 20 participants in 6 months. Descriptive statistics will be used to report the number of patients screened and determine rates of non-eligibility and refusal. Adherence for patients who are accrued to the study will be examined by calculating the degree to which participants are willing and able to complete the 30-minute VR exposure. 80% completed will serve as our feasibility benchmark. If less than 20% of consented patients complete the 30-minute VR exposure, the VR Blue protocol will not be considered feasible. Data completion will be measured by percent data collected at the study appointment, including pre-, midpoint and post-VR exposure assessments. 80% completed data will serve as our feasibility benchmark. If less than 20% of consented patients have complete data, the VR Blue protocol will not be considered feasible. Acceptability will be indicated by 80% of patients reporting satisfaction with VR Blue (mean score of 7 out of a total 8) on the Client Satisfaction Questionnaire. Safety of the VR protocol will be demonstrated 80% of participants completing the VR session without significant side effects, such as motion sickness, dizziness, headache, nausea, or other negative physical reactions. Analyses for Aim 2. We will examine descriptive data to explore pre-, midpoint and post-VR exposure changes in pain, tension and distress scores. We will cautiously examine these differences in the context of minimally clinically important differences (MCIDs) for pain, tension and distress (e.g., 30% decrease in pain).36-39 Correlations will be conducted to provide preliminary data on how pre- to post-VR changes

in two key cognitive variables (i.e., pain catastrophizing, pain self-efficacy) are related to improvements in pain, tension and distress occurring over the VR session. Analyses for Aim 3. Qualitative exit interview data will be coded using open coding and memoing by the study team to generate repeated concepts. These results will be categorized into major themes through selective coding methods. Grounded Theory methods will be used to evaluate the data gathered from the exit interviews.40,41 Results will be used to refine and improve the VR protocol for future studies. Dr. Somers (co-I) has used Grounded Theory in development of other psychosocial interventions for patients with cancer.

Risk/Benefit Assessment

Risks associated with the proposed study are minimal and not expected, but nonetheless will be carefully monitored. First, due to the use of virtual reality there is the potential for "cybersickness," a type of motion sickness involving feelings of nausea, eyestrain and/or dizziness. Anticipated risks associated with cybersickness are comparable to typical "everyday" use of computers. If the participant begins to feel any effect of this type, he/she may immediately stop the stop the VR exposure. Patients will be asked to report these symptoms and will have the option of discontinuing participation if these symptoms are problematic. Second, participants may experience anxiety or distress due to questioning about thoughts, feelings, and/or their experience with pain. Again, participants will have the option to discontinue participation if they experience such problems in completing the measures. Third, there is also the possibility of a breach of confidentiality. The informed consent process will address this possibility. All efforts will be made for confidentiality to be maintained by using study ID numbers to identify participants' research records and by having a limited number of individuals who have access to identifying information. Identifying information will be kept separate from research records. All research records will be kept in a locked file cabinet and password protected computer files. Only the PI and other trained research staff will have access to the research records.

All patients in the trial will continue their usual medical care during the course of the trial, thus their doctors will provide monitoring of the patients' overall medical status. Participants will not be asked to change or decline any strategies for pain management.

In terms of study benefits, participants may gain an enhanced ability to cope with pain and pain-related distress as a result of participating in this study. Further, participants may experience decreases in symptom severity.

The proposed significance of study findings outweighs the risks. The long-term goal of this research is to improve quality of life in advanced colorectal cancer patients by decreasing pain, tension and distress. This project will provide preliminary data that will be used to inform and optimize development of a multi-session VR protocol to be tested in patients with advanced stage colorectal cancer that could be generalizable to other palliative care populations with pain.

Data & Safety Monitoring

All research personnel who have direct contact with patients will be trained to observe and report any adverse events and unanticipated problems to the PI (Dr. Kelleher). The PI will review with her mentor, a

senior investigator, and will immediately report any safety/adverse events to the institutional review board at Duke University and to PCRC and NINR. An adverse event is defined as any untoward medical occurrence during the clinical investigation that has a causal relationship to the study protocol. A serious adverse event is defined as any event which results in death, is immediately life threatening, results in persistent or significant disability/incapacity, patient hospitalization, or is serious for any other reason representing significant hazard.