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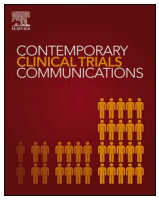

Virtual reality for management of cancer pain: Study rationale and design

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ABSTRACT

Background: Patients with cancer commonly experience acute and/or chronic moderate to severe pain related to disease, treatment, or both. While pain management strategies typically focus on drug therapies, non-pharmacological interventions may prove beneficial without risk of significant clinical side effects or contraindications. One novel strategy, virtual reality, has been shown to improve pain control in addition to usual pharmacological interventions.

Methods: This is a prospective, two-armed, single center randomized controlled study of a virtual reality intervention in 128 hospitalized subjects with cancer reporting pain rated at least 4/10 compared to an active control intervention, two-dimensional guided imagery. The primary outcome is change in self-reported pain score. Secondary end points include changes in self-reported distress, quality of life, and satisfaction with pain management. We will also explore patient preferences for distraction therapy content and themes through quantitative analysis of survey data, semi-structured interviews, and a collaging exercise.

Conclusion: This randomized controlled study aims to provide empiric data to support application and expansion of novel technologies such as virtual reality to augment usual pharmacological pain management strategies in hospitalized patients with cancer.

1. Introduction

Early integration of palliative care is recommended as a standard component of the treatment plan for any patient with metastatic cancer or who has a high symptom burden [1]. Over half of patients with cancer experience pain early in the disease course. The prevalence increases to 75% of patients as they progress through more advanced disease stages; additionally, 40% of survivors continue to suffer from chronic pain [2–4]. Despite treatment, pain is often severe enough to affect patients' ability to function, and both patients and providers agree that pain is poorly managed much of the time [5–8].

The American Society of Clinical Oncology (ASCO) guidelines for pain management in patients with cancer and in cancer survivors recommend pharmacological interventions [9]. Nevertheless, clinical literature and expert opinion also underline the importance of utilizing non-pharmacologic therapies to maximize relief without additional side effects [10]. However, these therapies are rarely available as a standard of care for hospitalized patients with cancer and those receiving inpatient palliative care consultation for pain management [11–14]. Furthermore, although many underserved populations with cancer, including some racial/ethnic minority groups, express interest in using non-pharmacologic therapies, access to these therapies remains limited [15]. Many non-pharmacologic pain management strategies are not reimbursed by insurance, limiting use to patients with disposable financial resources [16]. Aligning with emerging Joint Commission guidelines for hospital pain assessment and management, health systems must investigate non-traditional methods of supporting cancer patients with pain and ensure that these modalities are accessible and effective across a diverse patient population [17].

Of increasing interest to clinical practice and research on pain mechanisms and management strategies is the concept of distraction therapies. Distraction therapy can be any intervention that promotes competition between the individual's attention to active pain versus another activity that requires information processing [18]. The activity competing for the subject's attention – the distraction – can be passive (e.g. watching television, listening to music) or active (e.g. knitting, playing a video game). A common example of distraction therapy is guided imagery; clinical studies consistently demonstrate that guided

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imagery plus usual pharmacotherapy is superior to usual pharmacotherapy alone to mitigate pain [19–21]. The more engaging the activity for the individual, the more likely it will distract attention from the pain experience.

Virtual reality (VR) is an evidence-based non-pharmacologic distraction therapy that also continues to demonstrate effectiveness in acute and chronic pain management [22–24]. VR is a rapidly developing technology that can temporarily immerse the subject in a calm, pleasant environment, providing a distraction from pain and lowering pain sensation. Early clinical research in patients undergoing painful procedures such as burn wound care or dental procedures shows that brief VR sessions (e.g. 3–30 min) can lower self-reported pain scores, lower opioid drug use, and improve satisfaction with pain management [25,26]. While the pathophysiology of pain is complex, such non-pharmacologic interventions seem to modulate pain by reducing the level of attention paid to noxious stimuli, thereby suppressing transmission of painful sensations to the cerebral cortex [27,28].

The immersive nature of VR may create a more engaging form of distraction therapy compared to playing video games, listening to music, or engaging in two-dimensional guided imagery (e.g. rather than watching a video of a beach, one visually and acoustically experiences being at the beach). When used in addition to usual care (opioid and adjunct analgesics, with or without non-interactive distraction therapies), VR has been shown to provide clinically and statistically significant reduction in subjective pain score ratings [29,30].

Despite growing evidence of VR for pain management (particularly procedure-related pain, but also developing literature on chronic non-malignant pain) [31,32], there is limited evidence exploring its role in hospitalized adult patients with cancer. Outside of procedure-related pain, existing studies of VR in adult patients with cancer are limited by small sample sizes, homogenous patient populations and infrequent inclusion of a relevant distraction therapy control group. For example, VR was shown to reduce symptom distress, fatigue, and anxiety in 20 women with breast cancer receiving chemotherapy, compared to chemotherapy infusion without distraction therapy [33]. Other studies have investigated the effect of VR on time perception during chemotherapy infusion, but without any distraction therapy control group [34]. A recent study demonstrated the effectiveness of VR plus morphine to reduce pain and anxiety in 80 women with breast cancer in Jordan, compared to morphine alone [35]. Existing evidence underlines a remarkable opportunity to improve holistic care of adult patients with cancer for several important reasons: a) patients continue to request inclusion of non-pharmacologic strategies for pain management; b) hospitals lack adequate staffing and/or budget to consistently provide such non-pharmacologic approaches; c) health insurance plans rarely provide adequate reimbursement for non-pharmacologic pain management interventions, leaving patients to provide their own resources; thus, as VR technology rapidly evolves to deeper levels of immersive experience and affordable technology hardware including smartphones, patients, payers, and hospitals alike will be incentivized to employ such affordable non-pharmacologic interventions.

With funding from the American Cancer Society (http://cancer.org), we will compare the impact of a VR distraction therapy intervention on self-reported pain scores in hospitalized patients with cancer with that of an active control intervention, guided imagery delivered via a two-dimensional video experience (henceforth called two-dimensional guided imagery). Our Specific Aims are 1) to compare the impact of a VR intervention against an active control intervention (two-dimensional guided imagery delivered via portable tablet) on pain management measures for hospitalized patients with cancer who have baseline self-reported pain at least 4/10 (0 = no pain; 10 = worst pain); 2) to compare patient acceptance of and satisfaction with a VR intervention in patients with cancer against an active control intervention (two-dimensional guided imagery); 3) to explore patient preferences for distraction therapy content and themes through quantitative analysis of survey data of all subjects, and to explore explanations for these preferences through qualitative analyses of semi-structured interviews and collaging exercises for a subgroup of subjects to obtain explanations for these preferences.

2. Methods

2.1. Overall design

Our study is a prospective, two-armed, single center study of 128 hospitalized subjects with cancer reporting a minimum pain score of 4/10, randomized 1:1 to receive either a single 10-min VR session or a single 10-min two-dimensional guided-imagery session (active control). Following consent, subjects will be randomized using a computer-generated randomization scheme. The trial is unblinded since patients and the study coordinator cannot be blinded to the assigned distraction therapy.

The primary outcome is change in pre-versus post-intervention self-reported pain score using an 11-point numeric rating scale, framed by the question, “how do you rate your pain right now?” where anchors signify zero is “no pain” and 10 is “worst possible pain.” The duration of participation in the study is two consecutive days to allow for pre- and post-intervention surveys immediately before and after the one-time intervention as well as a follow up survey the next day. Given estimated hospital volumes, we anticipate the study will take one year for complete enrollment. The study has received institutional review board approval and has been registered at ClinicalTrials.gov (NCT04572074).

2.2. Study setting

MedStar Washington Hospital Center (MWHC) is a 912-bed tertiary referral academic hospital located in Washington, D.C. MWHC is also home to the Washington Cancer Institute, the largest cancer center in Washington, D.C.

This study will enroll hospitalized patients age 18 or older, living with cancer, who report pain 4/10 or greater within 24 h prior to consenting. Subjects will be excluded if they have intractable nausea/vomiting, history of motion sickness, history of seizures or epilepsy, have cranial structure or cervical spine abnormalities that prevent use of VR headset, are on contact isolation, are participating in another pain management study, and/or are unable to complete surveys in English. Because evolving literature suggests that analgesic benefits from VR use may linger up to 24 h [36], we also exclude those who use VR for personal use. These criteria were chosen to assist in the efficiency of enrollment by excluding any patients with medical conditions that may not allow for informed consent, may increase risk of harm or injury, or may interfere with or confound data collection.

2.3. Study intervention

VR sessions will be administered using the Facebook (Facebook Inc., Menlo Park, CA) Oculus Quest VR. This equipment was selected because it is portable and can be set up at the bedside in private or semi-private patient rooms. The hand controllers facilitate immersive, interactive VR experiences for patients who may be bedbound or have limited mobility in the inpatient setting. The VR software employed is the NatureTrek VR application (copyright Greener Games). This VR application features non-competitive experiences in natural environments (e.g. beach, rainforest, winter landscape) that can be played in a seated or fixed position (Fig. 1). Subjects will use over-the-ear headphones for sound and may use personal corrective lenses, including eyeglasses, or corrective hearing devices. In distraction therapy research, there is currently no predetermined time threshold for effect on pain experience; we chose 10 min for the intervention because it is a reasonably practical timeframe in a hospital setting and because it falls within the range of time frames (2–15 min) that have demonstrated benefit using VR for pain management [22,23]. Of note, we considered using

A.

B.

Fig. 1. Images from VR intervention (A) and two-dimensional guided imagery active control (B).

smartphone-based VR technology for this study, in which a smartphone is connected to a special viewing device through which the participant experiences VR; however, we believe that smartphone-based VR technology has not yet evolved enough to provide an adequately immersive VR experience to assure accurate results. We anticipate that high-quality, immersive smartphone-based VR will be available in the future as technology is developed and refined.

2.4. Active control

The guided-imagery session depicts a peaceful walk through a natural landscape with instrumental background music and a calm voice providing directions for a relaxation exercise (https://www.youtube.com/watch?v=6p_yaNFSYao#). (Fig. 1) Subjects will watch the guided imagery video on a portable tablet for 10 min, the same duration as the VR intervention. As with the intervention arm, subjects will also use over-the-ear headphones for sound and may use personal corrective lenses, including eyeglasses, or corrective hearing devices. We chose guided imagery as an active control to mimic other forms of distraction therapy that are readily available and could be viewed as more cost favorable.

All study devices (i.e. VR headset, tablet) will be cleaned with hospital-grade germicidal wipes by the study coordinator after each use, in accordance with hospital epidemiology recommendations.

2.5. Standard pain management

Subjects must have a self-reported pain score of 4 out of 10 at the time of the intervention. Subjects in both arms will continue to receive standard pharmacologic pain management. Subjects may continue scheduled long-acting opioids and non-opioid analgesics throughout study participation. To reduce the potential for confounding the analgesic effect from “as needed” opioids, the research team will conduct all research-related procedures (i.e., surveys, intervention) at least 10 min after administration of an intravenous opioid and/or at least 30 min after administration of a short-acting oral opioid. This will avoid overlap of the study intervention with expected peak analgesic effect from the opioid. We do not expect to demonstrate a reduction in opioid use in a patient population with chronic pain with a one-time study intervention but see this as a future area of study. Demonstrating that patients are accepting of and respond well to VR for pain management is the first step in making non-pharmacologic modalities readily available as alternatives or additions to current pharmacologic treatments.

2.6. Measurements

Our primary outcome will measure pre- and post-intervention self-reported pain score using an 11-point numeric rating scale, framed by the question, "how do you rate your pain right now?" where anchors signify zero is "no pain" and 10 is "worst possible pain." [37] We chose this outcome because self-reported pain scores remain the standard for clinical pain research, including research evaluating distraction therapies such as VR. Secondary outcomes will measure general distress, general quality of life, and satisfaction with pain management. General distress will be measured using the National Comprehensive Cancer Network Distress Thermometer (a Likert scale measuring from "No Distress" to "Extreme Distress," where "distress" is defined by the patient); to limit survey burden we are not including the associated NCCN Distress Thermometer Problem List [38]. General quality of life will be measured using the Functional Assessment in Chronic Illness-Therapy in Palliative Care 14-item scale (FACIT-Pal 14) [39].

Both groups will also be surveyed regarding acceptance of and satisfaction with the distraction therapy intervention itself and its thematic content and general content preferences for future distraction therapy experiences. Participants will view two-dimensional photographs on the tablet and will select three images they prefer best. Participants will also be surveyed regarding general preferences for computer-generated vs realistic imagery and interactive vs. passive distraction therapy content.

Patients who are randomized to VR will be asked to rate on a Likert scale the level of immersion of the VR experience ("To what extent did you feel present or like you 'went into' the virtual environment?").

In order to evaluate any potential residual effects of the distraction therapy, enrollees will be re-surveyed with self-reported pain score, FACIT-Pal 14, NCCN Distress Thermometer, and pain management satisfaction questions on the following day.

In collaboration with the MedStar Institute for Innovation National Center for Human Factors in Healthcare, we will also engage 24 subjects randomized to the VR therapy arm to participate in the exploratory qualitative inquiry (Exploratory Aim). The qualitative inquiry will be conducted in two phases such that we can share early findings with the Washington Cancer Institute Stakeholder Committee, obtain feedback, and identify additional areas of opportunity. Twelve subjects will participate in semi-structured interviews regarding the distraction therapy experience, visual and auditory thematic content of the therapy, and concepts of the idealized distraction therapy experience. Twelve additional subjects will participate in a collaging activity, a projective qualitative research technique in which participants select from a collection of visual or auditory samples (e.g. stock photos, magazine cutouts, music clips) to represent how they feel about a particular topic [40,41]. Exploratory in nature, this method builds empathy with participants and facilitates emotional understanding of their feelings and mindset [42]. In this case, it will allow participants to choose content that they associate with different experiences (e.g. feeling "relaxed," "safe," "at peace," "alive"). Participants then explain to the moderator reasoning behind their choices, allowing them to express feelings and needs that they may otherwise be unable to articulate. The result is a visual and auditory "collage," and an understanding of how best to design for the participants' true preferences. This technique is particularly valuable as images evoke strong responses in the participants, triggering memories and drawing out feelings that exist often below their own level of awareness. It encourages participants to genuinely share what is most meaningful to them [43].

2.7. Data collection

Participants will directly input survey responses using the Tonic Health platform on electronic tablets. All data will be password protected and de-identified prior to analysis. Results will be reported in aggregate by study groups. Participants will complete surveys immediately prior to the assigned distraction therapy experience and immediately after the distraction therapy experience, as well as the following day.

2.8. Statistical analysis

Our study will reach 80% power to detect a difference of 1 unit in the change in the pain score measure between the two groups using a two-sample *t*-test with equal variance at a two-sided alpha ¼0.05 and assuming a within-group standard deviation of 2 for each group (effect size ¼0.5). Sample size calculations were conducted in PASS. Baseline and outcomes data will be summarized using descriptive statistics such as means, medians and standard deviations for continuous variables and frequencies and percentages for categorical variables. Between groups comparisons will be tested using two-sample t-tests for continuous variables and chi-square or proportions test for categorical outcomes (Aim 1). Within-group changes will be tested using paired t-tests (Aim 2). Multiple linear regression analyses will be conducted to test the differences in the change of pain scores adjusting for potential confounders such as age, gender, severity of illness and baseline pain scores. We will also compare the rate of completion between both arms. Descriptive data will be used to report qualitative data related to feasibility and satisfaction. Data analyses will be conducted by the statisticians in the Department of Biostatistics and Biomedical Informatics at MedStar Health Research Institute.

For the Exploratory Aim, we will collect quantitative and qualitative data from participants regarding content preferences and distraction therapy experiences. Quantitative data will be obtained from study participant survey data to determine distraction therapy content preferences. Data will be analyzed using descriptive statistics and chi-square test. For the exploratory qualitative assessment, we will use purposive sampling to achieve an even distribution of patients by key demographics represented in at the study site; these include race/ethnicity, gender, and a range of ages to the extent possible given the sampling frame. We will perform descriptive analyses of demographic data and structured survey items related to feasibility and satisfaction with distraction therapy content and each participant's experience. Qualitative data from semi-structured interviews and collaging exercises will supplement and provide context for the quantitative survey data collected from all patients. These qualitative data will also generate emergent themes regarding distraction therapy content and preferences by patient demographics. Using a grounded theory approach, investigators will iteratively categorize and code data, comparing findings until a consensus is reached. Data from interviews will be analyzed using inductive reasoning and an interpretive approach. Data from collaging will also be thematically coded to generate sample mental models for the ideal VR experience.

3. Conclusion

Hospitalized patients with cancer commonly report untreated physical pain. Limitations offered by usual pharmacological therapies warrant exploration of non-pharmacological methods to augment relief, particularly those methods that can be developed to be patient-centered, portable, and easily scalable. This randomized controlled trial aims to provide empirical data to support application and expansion of novel technologies such as virtual reality to augment usual pharmacological pain management strategies in hospitalized patients living with malignancy.

Trial registration

ClinicalTrials.gov NCT04572074.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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