Immersive Multimedia as an Adjunctive Measure for Pain Control in Cancer Patients Research Protocol and Statistical Analysis Plan

Title	Immersive Multimedia as an Adjunctive Measure for Pain Control in Cancer Patients
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Name and contact information for the trial sponsor	Alona Nakonechnaya, Grants Manager, Lotte and John Hecht Memorial Foundation Email: ANakonechnaya@hecht.org
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Title: Immersive Multimedia as an Adjunctive Measure for Pain Control in Cancer Patients Research Protocol and Statistical Analysis Plan

Names protocol contributors

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Abstract

Background: Despite the growing popularity and affordability of virtual reality (VR), as adjunctive nonpharmacological interventions (NPIs) for chronic pain, there have been a few trials for effectiveness. his randomized controlled superiority trial, examined the effects of a home-based adjunctive VR NPI for chronic pain in cancer patients, compared to the same NPI experienced through a two-dimensional (2D) computer screen.
Trial Design: A parallel two arm participant blinded prospective superiority randomized controlled trial (RCT) with 1:1 allocation.
Methods:

- **Participants -** Community-dwelling adults with cancer-related chronic pain.
- **Interventions-** Home-based pain therapy through 4 applications involving cognitive distraction and mindfulness meditation for 30mins/day, 6 sequential days per applications for 4 weeks, either using VR or a 2D laptop.
- **Objective -** Determine to what extent virtual reality (VR) based applications are advantageous for daily home-based chronic cancer pain management compared to equivalent applications experienced on two-dimensional (2D) computer screens.
- **Primary Outcomes -** Daily and weekly pain scores measured via the Visual Analog Scale (VAS) and the Short Form McGill Pain Questionnaire (SF-MPQ).
- **Secondary Outcomes -** Weekly quality of Life (SF-12), and sleep quality (Pittsburgh Sleep Quality Index) were measured.
- **Randomization -** Used a Latin Square design (blocks of 12) to randomize participant arm allocation and sequence of applications experienced.
- **Blinding -** Single blinded (participants were blinded to which NPI they received).

Trial registration: Registered on 16/12/2016 at https://clinicaltrials.gov/ct2/show/NCT02995434?term=NCT02995434&draw=2&rank=1 Registration #: NCT02995434

Keywords

Chronic pain, virtual reality, chronic pain, cancer, cognitive distraction and mindfulness meditation.

Introduction

Background and rationale

This study sought to explore the efficacy of virtual reality (VR) as a practical therapeutic intervention in the self-management of the chronic pain associated with cancer survival. This work will inform further clinical studies and future research into the potential uses of VR in the treatment of cancer associated pain. Furthermore, it will help identify optimal VR environments for use in chronic pain applications, practical determinants for implementation of VR for wider practice, and will provide a better theoretical understanding of the mechanisms whereby VR works in chronic pain. Work in this area is in its infancy; VR represents a new technology that has many novel applications. Its value for pain control appears very promising and original clinical work is now essential to establish efficacy and optimal approaches. This proposal builds on results from our current pilot work, and review feedback.

Cancer survivorship refers to individuals who have remained cancer free for a minimum of 5 years.[1] Due to developments and greater outcomes associated with cancer therapy and management, the number of individuals who survive cancer has risen considerably over the past decade. Currently, 65% of adults and 80% of children can be expected to live at least 5 years post cancer diagnosis.[2] However, for some, survivorship is associated with debilitating chronic pain which impacts negatively on quality of life. Reviews have suggested that up to 40% of individuals have survived cancer remain with cancer related chronic pain.[3] Compounding this, chronic pain is poorly managed in Canada, and many patients are unable to access appropriate specialist treatment. Currently, in BC a conventional model underlies the primary provision of community-based chronic pain management, with most care being provided by family physicians, who refer their patients to pain management tertiary centers. However, access to these centers is severely limited due to capacity; a Canadian survey identified that six months was the median wait time, with more than 30% of centers reporting a wait list of more than one year, and vast areas of the country remained unserved.[4] While specialist pain centers management can be effective, this can only reach a small proportion of the chronic pain population. Furthermore, over the past couple of decades there has been a dramatic shift in emphasis in treatment, from treatment of acute to chronic disease, and more recently, the shift from physician directed management to patient self-management.[5] Novel approaches to community based patient self-management are therefore required.[6]

VR involves the provision of a synthetic environment that is experienced by a person through interactive sensory stimuli (audio-visual and sometimes touch) delivered by a computer interface in which the participants actions partially determine what happens within the environment. VR allows individuals to become active participants immersed within a computer generated three-dimensional virtual world, thereby transforming sensory, emotional and cognitive features of their experience. The phenomenon of becoming engaged in a virtual reality environment provides a powerful tool for behavioral and health scientists/professionals. VR can be used to immerse patients into different environments psychologically removing them from their existing physical reality. Computer-generated three-dimensional stereoscopic imagery simulates a visual 3D virtual world, with visual depth cues provided by perspective, motion parallax, rendered 3D objects and realistic textures. A Head-Mounted Display is used to present this world to the user, updated in real time using head (and sometimes body tracking) to simulate the realistic movement of objects with the user's motion. The 3D perspective is achieved by tracking the users head position so that imagery is updated from the perspective of each eye's location. To deliver immersive audio, stereo headphones or speakers are used to deliver stereo audio to simulate the location of the sound with respect to the position of the user's head. The combination of real-time 3D tracked imagery and audio presented in stereo enables the user to gain a sense of *immersion* and

presence inside the virtual world. By presenting the illusion that there is a virtual 3D world everywhere that the user looks, a very different experience is achieved than that of watching a flat screen. Exploration of the value of the latest generation of HMDs (now commercially available) with VR environments to support chronic pain has been little explored.[7] However, to date VR has been successfully tested in a range of clinical applications, and specifically in the treatment of acute pain, and with other conditions with a psychological aspect.[7] Outcomes for patients using VR for clinical conditions such as anxiety disorders,[8] phobias,[9] post-traumatic stress disorder,[10] eating disorders,[11] and pain management.[7]

VR is hypothesized to reduce pain via both active attentional and distractive mechanisms.[12] Neuromatrix theory suggests that pain is a multidimensional experience produced by a *neurosignature*, patterns of impulses generated by a widely distributed neural network, described as the "body-self neuromatrix" in the brain.[13] VR may work by changing the acuity of the pain modulation system by acting on the signaling pathways of this neuromatrix, producing an analgesic effect. Other researchers suggest that specific cognitive contextual mechanisms in the brain may also help mediate pain.[14]

Engaging in a virtual reality experience may therefore, change activity in the bodies' intricate pain modulation system, which in turn have an impact on pain perception. Here the anterior angulate cortex (ACC) region of the brain is suggested to be of particular significance in mediating pain and the ACC is suggested to mediate both attentional processes and emotional reactions in the personal perception of pain.[15] Given these theories, along with rapidly emerging technologies and clinical work in this field, it would appear that VR may have significant potential. However currently there has been little work done to establish the potential use of VR in the management of chronic pain to date, most work on VR for pain management has focused on acute pain via distraction. Several researchers have recommended the investigation of VR for chronic, long term pain[16,17] and the researchers are currently completing a pilot study to establish best methods and approaches to using VR in chronic pain conditions.

Objectives

This RCT aimed to determine to what extent VR-based applications are advantageous for daily home-based chronic cancer pain management, compared to equivalent applications experienced on two-dimensional (2D) computer screens. To this end, the following null hypotheses were tested:

1. There is no difference between the reported daily pain experiences of participants during, or after exposure to VR immersive environments, overall and within four different VR immersive environments, compared to the equivalent applications experienced on a 2D computer screen.
2. There is no difference in self-reported weekly pain, quality of life, and sleep experiences, of participants exposed to different VR immersive environments over the period of the study, compared to participants exposed to the equivalent applications experienced on a 2D computer screen.

Trial design

The study was a parallel two-arm (VR vs non-VR control) participant blinded prospective RCT with 1:1 allocation (clinicaltrials.gov, NCT #02995434). It was primarily conducted with rolling recruitment in British Columbia as well as Alberta, Ontario and Quebec between August 2017 and December 2022. The trial was approved by the University of British Columbia Clinical Research Ethics Board (Approval #: H16-01510), and all participants provided informed written consent.

Methods: Participants, Interventions and Outcomes

Study setting

Community - within patients' homes or residence.

Eligibility criteria

The inclusion criteria were:

- Aged >16, with a past or current diagnosis of cancer
- Past or current treatment with standard cancer therapies
- Experiencing chronic pain (ongoing daily pain ≥ 3 months with Neuropathic Pain Fidelity Scale ≥4 out of 10)
- Able to understand the English language (read and write)
- Normal stereoscopic vision
- Readily able to move head up, down, left, and right, and able to wear a headset
- Have fine motor control in one hand sufficient to use a game controller
- Have space at home for a computer and monitor

The exclusion criteria were:

- People who self-reported having significant cognitive issues, a history of seizures, claustrophobia, or high susceptibility to motion-sickness.

Who Takes Informed Consent?

Written consent was obtained by the project research assistant or primary/co-investigators as per ethical approval guidance from the UBC Behavioural Ethics Review Board from all participants before the trial commenced.

Interventions

Explanation for the choice of comparators

The phenomenon of becoming engaged in a virtual reality environment has been hypothesised to provide a more immersive and hence more powerful diversion experience to relief pain as an adjunctive NPI, placing patients into different environments psychologically removing them from their existing physical reality. [12] The adjunctive NPI involved two established approaches to chronic pain management: cognitive engagement and introspective mindfulness relaxation. [18,19] These activities were delivered through either an immersive VR system, or a laptop in the control arm. The VR equipment consisted of an HTC Vive (HTC, Taiwan) head mounted display (HMD) with a resolution of 1080x1200 pixels per eye, and 110° field of view at a 90 Hz refresh rate. Audio was delivered through the Vive Deluxe Audio Strap high-fidelity stereo headphones, and two hand controllers were used for application interaction, movement and navigation in the VR environment. Two infrared tracking modules enable 6-degrees-of-freedom spatial motion tracking of the HMD and controllers. The desktop computer running the VR system included hardware sufficient to run all activities at the highest graphical settings available for the applications. The non-immersive control arm participants received a 17" laptop with mouse, an XBOX game controller, and stereo headphones.

Intervention description

The VR equipment consisted of an HTC Vive (HTC, Taiwan) head mounted display (HMD) with a resolution of 1080x1200 pixels per eye, and 110° field of view at a 90 Hz refresh rate. Audio was

delivered through the Vive Deluxe Audio Strap high-fidelity stereo headphones, and two hand controllers were used for application interaction, movement and navigation in the VR environment. Two infrared tracking modules enable 6-degrees-of-freedom spatial motion tracking of the HMD and controllers. The desktop computer running the VR system included hardware sufficient to run all activities at the highest graphical settings available for the applications. The non-immersive control arm participants received a 17" laptop with mouse, an XBOX game controller, and stereo headphones. Two commercially available applications were used for cognitive distraction interventions. *Obduction* (OB: Cyan Ventures, Mead, USA) is a first-person adventure game that involved exploring a strange new environment, solving puzzles, and uncovering mysteries.

The other was *Cape Lucem - Seize the Light* (CL: Application Systems, Heidelberg, Germany). This was a VR puzzle game that involved manipulating and redirecting light beams in 3D space with different pieces to unlock objects. Participants used hand controllers to move puzzle pieces. Carpe Lucem was unavailable in a suitable format for laptop use, so another geometric puzzle solving application was used as a substitute for the control group, *The Witness* (WN: Thekla, San Francisco, USA). which requires participants to solve various maze-based puzzles.

Two mindfulness focused introspective applications were also used: *Virtual Meditative Walk* (VMW), and *Wildflowers* (WF). The VMW involved moving along a forested path while listening to a guided meditation for pain with accompanying relaxing music.[20,21] There were 3 meditations in sequence, and interaction in this activity was limited to looking around as the participant moved along the path.

The Wildflowers application involved controlling a butterfly from a third-person-perspective to explore a peaceful island. The participant could freely look around and control the butterfly's flight path three dimensionally using the controller. The application included locations for ten guided meditations, location-specific relaxing soundscapes, and interactive musical sculptures. Both applications were adapted by the developers for use in this project.

Criteria for discontinuing or modifying allocated interventions

Criteria for discontinuing included any serious adverse events as a result of the VR NPI (e.g., seizures, serious motion-cyber-sickness). Participants were able to change allocated NPI application (e.g., CL, WN, VMW, OB), if they found they provided a negative experience.

Strategies to improve adherence to interventions

Participants were required to record and notify the researchers of any change in the allocated application use and encouraged not to change the sequence of allocations, unless there was a significant issue. Practical support was provided through simple instructional materials and walkthroughs for the four different applications. A help service by phone, email or teleconferencing (with remote desktop computer access) was also provided for participants to contact a research assistant for technical support or any other issues they met during the trial. Participants were encouraged to contact them if anything seemed problematic or if they felt stuck.

Provisions for post-trial care

None, established standard of care was not altered as no pharmacological, invasive or potentially harmful interventions were used.

Outcomes

Primary Outcomes

Daily and weekly pain were the primary outcomes of interest. Daily pain was assessed using the Visual Analogue Scale (VAS). The VAS is a single item linear self-reported pain scale from no pain (0mm) to worst pain imaginable (100mm). It was selected as a well-established and validated subjective measure for acute and chronic pain.[22] The measure has demonstrated moderate-high correlation with the numeric pain fidelity scale (correlation coefficient from 0.62-0.91) 23 and high reliability (intraclass correlation coefficient = 0.97).[24] The clinically meaningful change for the VAS has been shown to be between 9mm and 12mm; this study adopted the convention of 10mm as the minimum clinically important difference (MCID).[25,26,27]

The Short Form McGill Pain Questionnaire (SF-MPQ) was used weekly to assess pain from baseline. The measure includes 15 items (rated not applicable, mild, moderate, severe) assessing sensory pain (11 items) and affective pain (4 items), as well as a VAS component scored out of 10. Higher scores mean greater pain. This instrument is also well-validated and established in clinical use,[28] and has demonstrated good sensitivity to change over time in chronic cancer pain.[29] An MCID has not been established for the SF-MPQ, although a clinically important change (CIC) has been identified as a mean total score of >5 out of the total of 55.[30,31,32] Its use here was designed to examine trends over the 4-week period of the RCT. A brief end of trial RCT survey was also completed by participants asking if they found any ongoing pain relief after NPI use (and if so, and for how long), if they reduced their pain medication requirements, if they helped or in other ways not captured.

Secondary Outcomes

The Health Survey Short Form (SF-12) was used as a self-reported outcome measure assessing health-related quality of life weekly.[33,34] It includes 12 items with binary response items and 3-6-point Likert items. The SF-12 is scored using proprietary software to generate a physical composite (PCS) and mental composite (MCS) health scores ranged 0-100, with scores above or below 50 indicating greater or poorer health than normative mean, respectively. The measure has demonstrated validity (internal consistency $\alpha_{PCS12} = 0.89$; $\alpha_{MCS12} = 0.88$) and reliability ($ICC_{PCS12} = 0.82$; $ICC_{MCS12} = 0.73$) in a sample of 420 adult cancer patients.35 MCID is smaller in patients with longer pain duration and better baseline quality of life, and based on prior medical studies a MCID >3.77 in the MCS and >3.29 in PCS, were adopted as clinically relevant for this study.[36,37]

The Pittsburgh Sleep Quality Index (PSQI) was used as a self-reported outcome measure assessing sleep quality on a weekly basis.[38,39] The measure includes 19 items asking about sleep schedule, duration, disruption frequency (4-point Likert scale), and quality (4-point Likert scale). Scores range from 0-21, with higher scores indicating worse sleep quality. The PSQI has demonstrated validity in cancer patients with Cronbach's alpha ranging from 0.77-0.81.[40] Estimates for the MCID for the PSQI index score range from 1.3 to 4.4.[41]

Potential Moderator and Exploratory Outcomes

As no suitable tool was available when the RCT commenced, a simple 28-item immersion survey instrument was developed based upon prior work exploring immersive fidelity (quality of audio-visual representation on sense of immersion in the environment) and presence (sense of dislocation from the real world and being present in a virtual world).[42,43] Items used 5-point Likert scales, with two global items assessing immersion and presence on 10-point Likert scales. This survey incorporated the previously validated Immersion Experience Questionnaire (IEQ)[44] and was administered at the end of

each week of the trial. Potential moderator demographic variables were also collected including age, gender and type of cancer. Any reported cybersickness (VR-induced motion sickness) was recorded by participants weekly on a 5-point Likert scale, with an option to add comments.[45,46,47]

Participant timeline

During the trial, each participant engaged in a daily 30-minute immersive media therapy session in their own homes, either as a VR activity or a screen-based laptop activity for the control group. The NPI was used every day for a month, using one of four different applications for a week each starting on a Monday, for six days in sequence. There was a one-day rest/washout period on Sunday at the end of the week before changeover to the next application (Figure 1).

Equipment was initially set up in the participant's own home at the start of the month, and orientation and training provided involving a detailed overview of the study, instruction and provision of a data collection binder with daily and weekly measures, as well as familiarization with equipment and applications. The binder was sectioned into each week, with daily sheets including instructions to record the time spent each day, and their pre, during, and post exposure VAS pain scores. To avoid the effects of interrupting the immersive activity, participants were asked to complete the "during" VAS pain score immediately after the session by "thinking back to somewhere in the middle of your session and fidelity your pain at that time." Participants were supplied a timer they were asked to set for 30-minutes; however, they were told this was a minimum and that if they wanted to spend more time to complete their puzzle or task, they were welcome to. At the end of each week, participants completed the SF-12, PSI, SF-MPQ, and the Immersion/Presence survey, including cybersickness fidelity and any deviations from the binder. The end-of-study questionnaire included the option to add comments on how useful they found the NPI overall and any other thoughts they wished to record about the therapy.

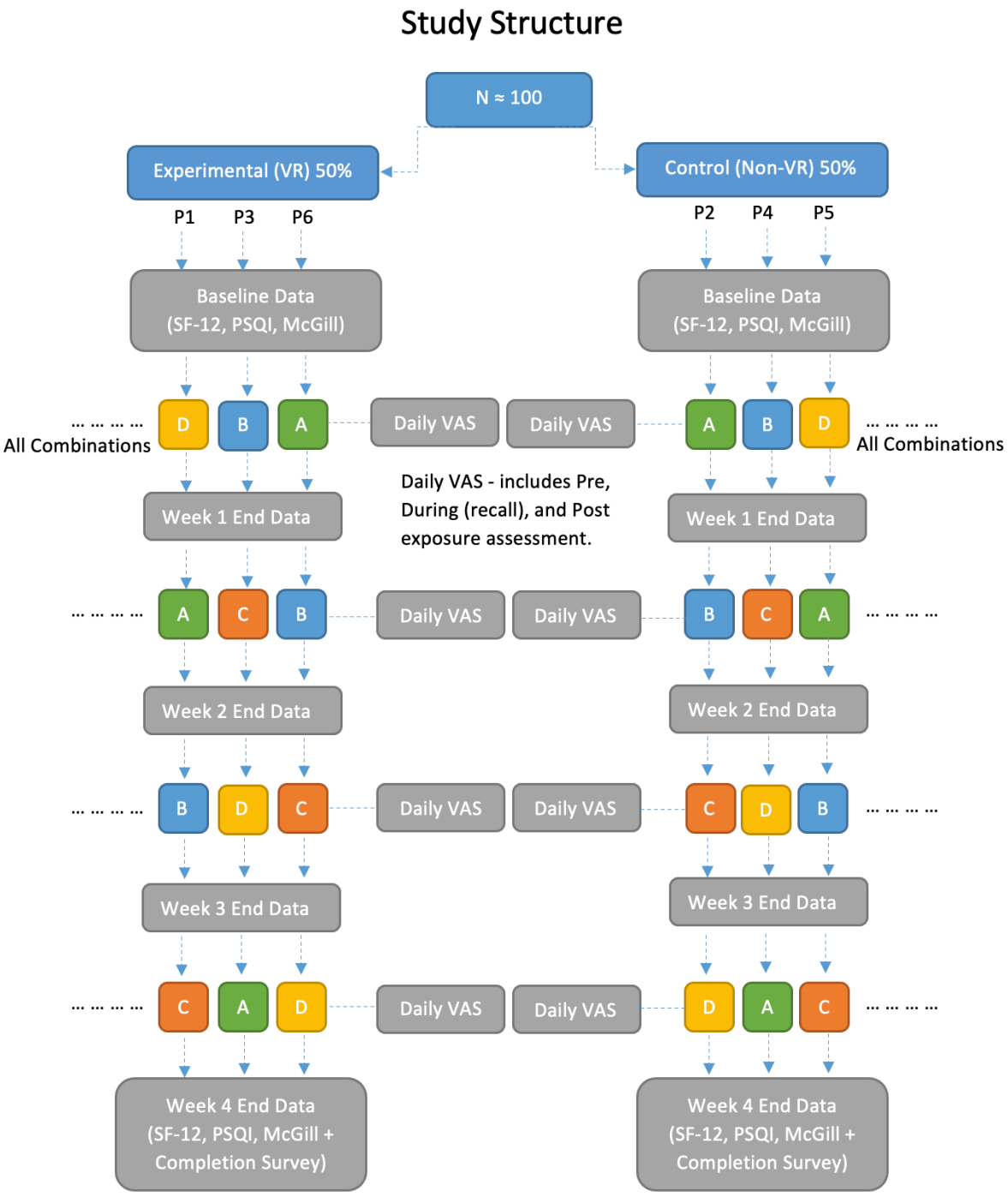

Figure 1: Study Participant Timeline.
Notes: A,B,C,D are the matched VR/Non-VR Activities undertaken, i.e., OB, VMW, WF

Sample size

Sample size was determined by a power analysis to test group differences in pain intensity between two arms. Due to limited recruitment feasibility, a third *no intervention* arm was impractical, and the two arms were considered sufficient to establish the impact of VR as a discrete pain therapy. As reliable estimates of expected effect size were unknown, the study was powered to detect a medium effect (0.5 SD change), considered a reasonable clinically meaningful impact to obtain 80% power based on a repeated measures analysis of variance (RM ANOVA) with 2-tailed alpha of .05 model. [48] Power calculated using the G*Power application suggested a minimum sample size of 100 participants (50 in each group).

Recruitment

Community-dwelling adults with cancer-related chronic pain were recruited through postings in cancer clinics, pain clinics, hospitals, support groups, support networks (PainBC, People in Pain Network), physician networks, social media, and the REACH BC research volunteer website. Initial recruitment focused on BC. Recruitment was expanded to Alberta in 2020 and Canada-wide in 2022.

Assignment Of Interventions: Allocation

Sequence generation

Applicants were screened for eligibility and assigned a participant ID by the research coordinator. The research assistant responsible for equipment setup would then determine the participant's group from the assignment sheet. Participants were randomly assigned to either the VR or control group in blocks of 12 using a Latin Square design assignment sheet prepared by a professional statistician. Each block of 12 included six unique permutations for order of the NPI applications used to effectively randomize allocation and avoid sequencing effects.

Concealment mechanism

Arm allocation (VR or control) was concealed to applicants, who were informed they were taking part in a multimedia pain-relief study, not a VR study.

Implementation

Arm allocation and NPI allocation sequence was undertaken by the research assistants.

Assignment Of Interventions: Blinding

Who were blinded

Participants only were blinded to allocation and sequence (single binding) as it was not possible to conceal treatment allocation by the research team.

Procedure for unblinding if needed

None, as no pharmacological, invasive or potentially harmful interventions were used.

Data Collection and Management

Plans for assessment and collection of outcomes

Participants used a written data collection binder with daily and weekly measures, as well as familiarization with equipment and applications. The binder was sectioned into each week, with daily sheets including instructions.

Each day participants recorded their pre, during, and post exposure VAS pain scores, and the time spent using the NPI. To avoid the effects of interrupting the immersive activity, participants were asked to complete the "during" VAS pain score immediately after the session by "thinking back to somewhere in the middle of your session and fidelity your pain at that time."
At the end of each week, participants completed the SF-12, PSI, SF-MPQ, and the Immersion/Presence survey, including cybersickness fidelity and any deviations from the binder. The end-of-study questionnaire included the option to add comments on how useful they found the NPI overall and any other thoughts they wished to record about the therapy.

Plans to promote participant retention and complete follow-up

Participants who withdrew from the study, were asked to provide a reason for withdrawal (this was not compulsory). Data from partially completed participants was included whenever possible when sufficient for quantitative statistical analysis

Data management

A current list of the names of study personnel (including coinvestigators and research staff) and their delegated tasks was maintained in the study file. Personal data was be kept solely on a UBC networked encrypted computer data storage. Drs. Garrett, Gromala and Taverner had access throughout the study (and the PI and CI to the archive thereafter). The Project Manager and research assistants had access to the data during the course of their employment on the project with UBC.

Confidentiality

Only the consent forms had the participants identification, and the electronic password protected key data file with names and subject numbers. Thereafter participants were referred to by Research subject identifiers (numbers) only not derived from any existing personal identifiers (e.g., SIN). The consent forms were kept in a locked cabinet in the principal investigator's locked office. All participants were issued with a study number identification, this number were used on all data collection files and data spreadsheets, analysis and reporting. A password protected file with contact details and addresses were kept on an electronic file, this were password protected and kept on a computer at UBC.
Only the researchers identified on this ethics approval will have access to the data. All physical documents and files pertaining to this study were identified only by code number and kept in a locked filing cabinet in a locked office in the UBC School of Nursing. Apart from the password protected single key data file, all data stored on electronic media (computers) at UBC's School of Nursing did not include the name or personal details of the individual subject.

Statistical Methods

Statistical methods for primary and secondary outcomes

A first exploration of all outcomes across all participants was undertaken, using an intention to treat analysis (where all participants were included in the statistical analysis and analyzed according to the group they were assigned, regardless of individual changes in protocol). For the primary outcomes of interest, a minimum clinically important difference (MCID) of 10mm on the VAS scale was adopted. The data exploration also found highly varied pain experiences by many participants throughout the trial, with many beginning their daily activity with pain below a 40mm VAS score, or even with no pain on some days. Hence, a further sub-group analysis was undertaken excluding data from participants whose pre-exposure VAS score was less than 40mm on that day, to explore for effects in this sub-group of participants who were experiencing more substantial pain at the time of the NPI exposure.

Linear mixed effects modelling was used to establish whether there were differences in the outcomes of interest between the VR and control groups. Patient-level random effects were considered to account for the repeated outcomes measures. Interaction terms of participant exposure and time were included in each model and used to ascertain whether changes in the outcomes of interest from baseline - before each activity for the daily and before exposure to NPI for the weekly outcomes and at specific time points – during and after each activity for the daily and at day six for the weekly outcome measures – were different between the VR and non-VR groups. Baseline demographic characteristics and duration of exposure to each environment for the daily outcomes were considered for adjustment in the full models. Terms were sequentially removed from the full models if their exclusion did not affect model fit. Reduced models were compared to full models using the Akaike Information Criteria (AIC) and those with the lower values were identified as the final models for each outcome. Using the final models, adjusted values of each outcome per group were estimated and presented as mean summaries with standard errors as a measure of dispersion. The 95% confidence interval (CI) of the fixed effects were estimated using the bootstrapping method and graphical plots of residuals and fitted values were used to determine whether normality and constant variance assumptions were met. To explore potential correlations between video and audio fidelity, and cyber sickness between applications in the immersion survey a two-sample t-test was also used. All analyses were conducted using R statistical software. For more details on the statistical analysis plan, please refer to Appendix A.

Interim analyses

An interim analysis was completed in 2021 (n=52) and indicated no substantive difference between arms, and no significant adverse events. The study was continued to achieve the intended sample size.

Methods for additional analyses (e.g., subgroup analyses)

For the primary outcomes of interest, a minimum clinically important difference (MCID) of 10mm on the VAS scale was adopted. The initial data exploration also found highly varied pain experiences by many participants throughout the trial, with many beginning their daily activity with pain below a 40mm VAS score, or even with no pain on some days. Hence, a further sub-group analysis was undertaken (using the same methods outlined above) excluding data from participants whose pre-exposure VAS score was less than 40mm on that day, to explore for effects in this sub-group of participants who were experiencing more substantial pain at the time of the NPI exposure.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data

A complete case analysis was conducted as there were few participants (<5%) with missing data.

Plans to give access to the full protocol, participant level-data and statistical code

This protocol is publicly available from the clinicaltrials.gov website, or from the primary researcher on request.

Oversight and Monitoring

Composition of the coordinating centre and trial steering committee

Primary Investigator and Project leader: Dr. Bernie Garrett: responsible for overall project leadership, management, and staffing.

Co-Investigators: Dr. Tarnia Taverner and Dr. Diane Gromala: oversaw project management with bi-weekly review meetings, and assisted in data analysis, and report writing.
Project Coordinator: Crystal Sun (oversaw day to day project management, coordinated b-weekly meetings, managed financial accounts and report writing)
Research Assistants: Gordon Tao (PhD Candidate), Elliot Cordingly: (undertook VR installation set up, take-down collected data binders, provided participant support and assisted in data cleaning and collation for analysis, and report writing.
Statistician: Richard Musoke (PhD Candidate): Undertook statistical analysis, data cleaning and collation for analysis, and report writing.

Composition of the data monitoring committee, its role and reporting structure

As a small scale trial (with no more than 6 participants participating at any one time) a secondary DMC was not required.

Adverse event reporting and harms

A weekly form for reporting adverse events was required to be completed by all participants. In addition, participants were biased to report any substantive negative experiences or adverse events by telephone to the provided research helpline immediately.

Frequency and plans for auditing trial conduct

The independent UBC Behavioural Research Ethics Board was able to audit the study at any time to ensure practices were carried out in accordance with the ethical approval certificate. No audit was carried out during the course of the study.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees)

All changes to eligibility, recruitment methods, procedures, outcomes, analyses were reported to the UBC BREB for review and approval as post-approval activities, and all changes amended on the clinicaltrials.gov site.

Dissemination plans

This study supports a knowledge translation (KT) process designed to develop theory based on pre-existing innovation, and further define the practical determinants, implementation and uptake considerations for VR use in wider practice. The primary KT target audiences will be healthcare professional groups involved in the management of chronic pain, patients experiencing chronic pain, and their relatives, although we will be careful to avoid prematurely claiming our study findings as generalizable. Health Professional academic/clinical conference presentations will also be undertaken, and it is planned at least three peer-reviewed publications in professional journals will be produced. In addition, a publicly accessible project summary will be sent to all participants and a project website with video and text based resources related to the work has been established at https://blogs.ubc.ca/arvrha/ where the final report will be posted, with links to the publications arising from it.

Discussion

Due to the global COVID-19 pandemic, the study was paused completely between March 2020 to June 2020. The study was paused two more times (November 2020 - July 2021; Dec 2022) due to pandemic conditions. From June 2020, the study restarted with modified protocols to minimize physical contact and ensure safety according to Behavioural Research Ethics Board guidelines. Participants were screened for COVID-19 exposure and symptoms before each contact. Baseline demographic and outcomes data collection was moved from the set-up session to a teleconference interview session to shorten the session. Participants also received online videos for equipment training to review before the study visit. The set-up session was modified to require personal protective equipment and 2-metre distancing between RA and participant, relying on verbal instructions and demonstrations observed at a distance for training. Weekly check-ins also included screening for COVID-19 symptoms and reassessment of consent. At the end of the participant's 4 weeks, equipment was disinfected during collection then stored in a secure room for 4 days before preparation for use by another participant. When we expanded recruitment across Canada in 2022, we modified the set-up protocol to be completely remote. For participants located outside of BC, participants were shipped all study equipment. For VR, participants received a high-end gaming laptop that could run all VR environments at the highest graphical settings instead of a desktop computer. Participants were asked to view a brief tutorial video on how to set up the equipment. Once the participants received the equipment, an RA would conduct the set-up session via teleconference.

Declarations

Acknowledgements

We acknowledge Dr. Diane Gromala, Dr. Christopher Shaw, and their graduate students at the Pain Studies Lab at Simon Fraser University for the development of Virtual Meditative Walk, one of the environments used in the study, and their continued support and collaboration throughout the project. We also acknowledge the support of Dr. Bechara Saab, at Mobio Interactive for the development and use of Qualia Wildflowers (WF), Cyan Worlds for Obduction (OB), and Hammer Labs for Carpe Lucem (CL) by supporting free use of their VR applications in the study. We thank Dr. Pippa Hawley and Dr. Gil Kimel for their support with participant recruitment at BC Cancer centres and at St John Hospice. We also thank the Lotte and John Hecht Memorial Foundation for their funding to conduct this research (Grant ID: 4110). The funding source has no authority in the study design or execution or in this manuscript's preparation. Lastly, we want to thank all the participants in this research study for their time and effort, without whose participation this work would not have been possible.

Authors' contributions

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Availability of Data and Materials

Public access to the final trial dataset, which is available for free academic use is authorized by the researchers. These data are available from clinicaltrials.gov, the open access publications arising from this work, and from the authors by request. Previous open access publications related to this work include the following:

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Ethics approval and consent to participate

Ethical approval for the study was granted by the UBC, behavioural research, ethics, board, (certificate number H16-01510). Written, informed consent to participate were obtained from all participants prior to participation and data collection.

Consent for publication

The authors listed above consent to the use of the publicization and use of this protocol for academic use. A model consent form is also available.

Competing interests

The authors listed above declare that they have no competing interests.

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Appendix A – Detailed Statistical Analysis Plan

1. Objective

Determine the extent to which VR-based applications are advantageous for daily home-based chronic cancer pain management, compared to equivalent applications experienced on two-dimensional (2D) computer screens.

2. Outcomes

This section presents the outcomes investigated to answer the study objective. The analyses are described in section 3.

Primary outcomes

Visual analogue scale pain scores from 0 to 100mm measured before, during and after an immersion for 24 days.

Weekly pain scores measured using the McGill Pain Questionnaire separately for each component sensory pain (11 items), affective pain (4 items), Visual Analogue Scale component scored out of 10 and overall, as a sum for all three components measured at baseline and at week 1, 2, 3 and 4.

Secondary outcomes

Health related quality of life scores measured using physical and mental health components of the short form quality of life questionnaire and the sleep quality index measured using the Pittsburgh Sleep Quality Index all measured at baseline and at week 1, 2, 3 and 4.

3. Population and Subgroup Analyses

Populations

Intention-to-treat (ITT)

All randomized participants will be included in the analysis as allocated to either the intervention or control arm.

Sensitivity analysis

A subgroup analysis of participants with pain scores before an immersion session will be conducted. Analyses for this population will be used to investigate whether conclusions are sensitive to severity of pain before an immersion session.

Subgroup analyses

Four sub-analyses will be conducted for each application. All sub-analyses groups will be conducted for the overall sample and for the sample with severe pain.

4. Data analyses

All outcomes will be presented using descriptive statistics; normally distributed data by the mean and standard deviation (SD) or standard errors (SE) and binary and categorical variables will be presented using counts and percentages. R software version 2.4.3 will be used for all statistical analysis.

The sections below describe analyses that will be conducted in addition to the descriptive statistics.

Primary outcome

The primary analysis will compare mean changes in daily pain before each immersion session and pain scores during and after each session in intervention group to mean changes in daily pain before each immersion session and pain scores during and after each session in control group. Difference in pain score before to time points where it is measured during and after each session (during and after) will be the dependent variable. Study participants will be considered as random effects, treatment group and time together with an interaction term of the treatment group and time as fixed effects. The estimated difference in mean change from before to during, and after immersion sessions and the corresponding 95 % confidence interval (CI) between groups will be presented.

Using a similar approach, the mean changes in weekly pain from baseline measured using the McGill Pain Questionnaire for the overall pain score – combining assessing sensory pain (11 items) and affective pain (4 items) as well as a VAS component scored out of 10, and separately for each component – in intervention group to mean changes in weekly pain in control group will be compared.

Secondary outcomes

Mean changes from baseline in weekly health related quality of life scores and sleep quality index measured using the Health Survey Short Form quality of life and Pittsburgh Sleep Quality Index respectively were compared between the intervention and control groups using the approach like that of weekly primary outcomes.

5. Missing data

When analyzing data for all study participants and those with severe pain, complete case analyses will be conducted for both primary and secondary outcomes. If the number of participants excluded due to missing demographic characteristics is >5% comparisons by assignment arm of those included and those excluded will be conducted to determine if there are any differences in drop out by arm.

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