**Virtual Reality pain psychology therapy as non-pharmacological analgesia for cancer-related chronic neuropathic pain**

**(The VIPER-C study)**

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**2. SYNOPSIS**

This is a pilot feasibility study of pain psychology therapy delivered by virtual reality to cancer patients with chronic pain.

Non-pharmacological pain management strategies are recommended by the 2010 Australian National Pain Strategy, the 2016 Australian Adult Cancer Pain Management Working Group, and from the Cancer Council of Australia. This includes the use of pain psychological methods, which aim to improve the patient’s cognitive and emotional adaptation to pain.

Virtual reality (VR) is the visual and aural projection of a software program onto goggles and headphones worn over the user’s head. This creates an immersive experience for the user as external visual and auditory cues are replaced by what is projected onto the VR goggles and headphones. Users interact within this projected VR environment through the use of hand-held motion controllers, by manipulating objects or choosing options. VR is most commonly associated with computer games and videos. The evidence-base for medical applications of VR remains in an early stage.

In this research program, a VR software to deliver a suite of pain psychological therapies has been custom-made. This is a unique software that codes for a suite compromising three distinct modules; (1) a pain education module, (2) teaching the method of progressive muscle relaxation, and (3) pain visualisation therapy. These non-pharmacological analgesia adjuncts seek to reduce reliance on pain medications, and improve functional outcomes. Previous attempts at VR-delivered pain management were replays of distracting movies, and was not interactive or proposed long term psychological therapy.

The primary objective of this prospective pilot study of 40 patients is to confirm feasibility and acceptability of VR use in a cancer patient population with chronic pain. The secondary objective is to obtain initial effectiveness results on pain scores, opioid consumption, and functional activity, from this novel method of non-pharmacological analgesia.

**3. RATIONALE / BACKGROUND**

3.1 Pain Management Principles

Inpatient pain management includes pain medications, invasive pain procedures, and non-pharmacological methods. Opioids have traditionally been mainstays of pharmacological therapy, but have significant and numerous side effects and risks.1 Opioid drug analgesia alone has been implicated in problems including dependency, overdosage, constipation, respiratory depression, tolerance, cognitive disturbances, delirium, paradoxical hyperalgesia, immunomodulation, societal abuse, diversion, and mortality. Pain procedures such as intrathecal catheters for continuous drug delivery, sympathetic blocks, electrical neuromodulation, and surgery, also have risks due to their invasive nature.

There are several types of non-pharmacological analgesia modalities. They include pain psychology therapies, transcutaneous electrical stimulation, and acupuncture. Usually, these non-pharmacological methods are used in the context of a multimodal analgesia care plan. The goal of non-pharmacological analgesia is to act as adjuncts, reducing the consumption of medications, reduce the need for invasive pain procedures, and to improve functional outcomes in activities of daily living, quality of life, and emotional state. It is rare for non-pharmacological therapies to be the sole method to treat moderate to severe pain.

There are multiple pain psychology therapies available. These can be categorised into 4 broad types: information provision (pain education), relaxation techniques (arousal reduction therapy), distraction and mindfulness (attentional therapy), and techniques to reduce pain catastrophising and functional disability (cognitive-behavioural therapy).2 These categories are not exclusive and commonly overlaps. The basis for the effectiveness of pain psychological therapies is through improving the patient’s cognitive and emotional adaptation to pain.

However, psychologists trained specifically in pain psychology are traditionally required to deliver therapy, typically during one-on-one sessions. It is thus resource-intensive and access to this helpful adjunct may be limited. More recently, VR-delivered pain psychological therapy has been used, albeit primarily as a distraction method through the use of passively viewing videos.

Potential advantages of VR-delivered pain psychology therapy includes:

(1) scalability: pain psychological therapy is limited only by the number of VR goggles available. In contrast, there is a limit to the number of available human therapists in any hospital;

(2) accessibility: patients can undergo therapy at their time and location, rather than being restricted by availability of a human therapist (especially in rural and remote locations) and their appointment schedule;

(3) repeatability: patients can repeat their therapy sessions at any time, rather than being restricted by a set appointment schedule;

(4) Cost-effectiveness: VR equipment is relatively cheap compared to salary costs and travel, and the capital expenditure is balanced by re-usability.

3.2 Using Virtual Reality in Pain Management

Efficacy of VR psychological therapy in randomised controlled trials have shown benefit in selected patient populations. Six studies used VR to alleviate transient noxious procedural pain (burns dressing change, paediatric venous cannulation and vaccinations), with most reporting reductions in pain scores and doses of rescue opioid analgesia.3-8 Gold et al however did not find any benefit when comparing VR versus topical anaesthesia for paediatric cannulation.9 One study in chemotherapy patients showed reductions in anxiety and nausea, but opioid consumption and pain score data was not collected.10 In contrast, Bani Mohammad did find reductions in opioid consumption and pain scores in chronic cancer pain patients.11

Notably, these studies have small sample sizes, are methodologically heterogenous, and do not have comparable outcome measures. Previous studies also relied on passively viewing an exciting or calming video clip during their VR sessions. These interventions are thus best classified as transient distraction methods, and longer term benefits were not assessed after the passive VR intervention had concluded.

In contrast, “active” VR pain psychological therapy has not been a prior area of research. To explore the potential efficacy of this type of therapy, we therefore created a new VR software program that incorporated the following three pain psychological modules:

(1) Patient education on the nature and type of pain, and methods to control pain;

(2) Teaching progressive muscle relaxation as a form of arousal reduction therapy; and

(3) Guided pain visualisation technique to reduce pain catastrophising, reduce maladaptive response to pain, and improve functional outcomes

These modules are selected by patients using their hand-motion controllers. Patients can advance, stop, or rewind the therapy. An electronic representation of a therapist (“avatar”) is projected through the VR goggles that will speak with the patient. Patients are required to be active participants, interacting with the avatar by choosing their therapy options in real time.

Screenshots from our VR-pain control therapy is illustrated below. Figure 1 is the therapy environment that patients are placed in to interact with the avatar, Figure 2 is the relaxation therapy environment, and Figure 3 illustrates the different pain character emotions used during guided pain visualisation.

The interaction between patient and VR-pain control therapy does not require external intervention from a psychologist. However, the view experienced by the patient is projected onto an external TV. This will be monitored by a researcher, who can intervene if necessary.

The pain psychology therapy content in our software is informed by expert pain psychologists from Innervate Pain Management, Newcastle. The coding of the VR-pain control therapy is in collaboration with cognitive and computer scientists from the MARCS Institute of Brain, Behaviour and Development, Western Sydney University. The VR software is created with the Unity software package, allowing future compatibility with commercial VR devices.

Grant funding for VR software development was awarded through an external, peer-reviewed competitive process, administered by Sony Australia and the Tour de Cure Foundation, in 2018.

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Figure 1. a) Therapy room b) Garden environment 1

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**** Figure 2. a) Garden environment 2 b) Beach environment

****Figure 3. Examples of emotions experienced by the projected pain character, displayed during the VR guided pain visualisation therapy. Burning pain, sharp pain, anxiety emotions are being displayed. The character mimics changes according to patient interactive input on their level of experienced pain, with the aim of guiding towards pain acceptance and behavioural modification.

3.3 Cancer-related chronic pain

Chronic pain is reported by up to 75% of cancer patients.12 Despite an improvement in understanding of cancer pain, 25-55% of these patients still report an undertreatment of their cancer-related chronic pain.13 The large variability may be in part due to national and regional variances in access to medical therapy and therapeutic options. There is also a variability associated with the type of cancer, the anatomical location, and pain associated with cancer therapy (chemotherapy, radiotherapy, and surgical procedures). As a consequence, best practice involves a multimodal approach that integrates different analgesic options. However, availability of non-pharmacological options are often restricted due to the need for specially trained health professionals.12

One specific aspect of cancer-related chronic pain which is difficult to treat is neuropathic pain. Neuropathic pain may be caused by the cancer itself due to direct tumour involvement or nerve impingement by an expanding growth, paraneuroplastic neuropathies, surgery for cancer, radiation therapy plexopathies, and chemotherapy related side effects causing painful peripheral neuropathies. The Agency for Clinical Innovation (ACI)/NSW Health notes that neuropathic pain is complex in nature, is patient specific, difficult to diagnose, and requires a combination of treatment modalities including non-pharmacological methods.14

This research study will recruit patients with cancer-related neuropathic pain. This pain may be directly associated with their cancer, or as a complication of chemotherapy (especially platinum and taxane-based medications), or radiation therapy. This patient population was selected due to regular oncology clinic visits to the Liverpool Hospital Cancer Therapy Centre, and experiencing chronic pain for which psychological pain management therapy may be of benefit.

**4. AIMS / OBJECTIVES / HYPOTHESES**

1. Assessment of side effects from the use of VR-pain psychology therapy, to establish feasibility and acceptability of VR use in a clinical setting.

2. Evaluation of effectiveness of VR-pain psychology therapy as a non-pharmacological adjunct to conventional analgesia management in a chronic neuropathic pain, cancer patient population.

**5. PARTICIPATING SITES**

Liverpool Cancer Therapy Centre, Sydney

**6. RESEARCH PLAN / STUDY DESIGN**

6.1 Type of study

Prospective, blinded, randomised controlled trial, pilot feasibility and effectiveness study of VR-delivered pain psychology therapy (“VR-therapy”) in cancer patients with chronic neuropathic pain.

● Inclusion Criteria:

Adult (≥ 18yo) patients with cancer, and with the following characteristics:

- Eastern Cooperative Oncology Group (ECOG) score 0-2

- Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) score ≥ 12

● Exclusion Criteria:

- Insufficient written English language proficiency to complete questionnaires.

- Insufficient verbal English language proficiency to interact with the VR software avatar.

- Psychological or psychiatric illness not stabilised with therapy and/or medications.

- Uncertainty or unable to be followed up for subsequent six months after recruitment.

6.3 Population/Sample size

No previous studies have used active pain psychology therapies delivered via VR. A convenience sample size of 40 patients will instead be recruited, divided into 20 patients each in the intervention and control arms.

Patients in the intervention arm will receive 3x 30min sessions of VR-pain psychology therapy. Each session will allow one module of the VR-pain therapy to be provided.

Patients in the control arm will receive 3x 30min sessions of VR-delivered distraction therapy in the form of movies/videos filmed in VR. All movies are publicly accessible through the dedicated VR channel from YouTube. Example movies that can be chosen by the patient includes a documentary on jaguars in Brazil (<https://www.youtube.com/watch?v=1DdGPtSVncg&list=PLU8wpH_LfhmvMe2QPJpNnrUB4mlSC6QCw&index=45>), a documentary on the Apollo 11 moonlanding (<https://www.youtube.com/watch?v=5RI9kymFeYM&list=PLU8wpH_LfhmvWzER0Cb8AFxvpmUKMTvPU&index=36>), an animated cartoon in a snow environment (<https://www.youtube.com/watch?v=DR1gT36OtJQ&list=PLU8wpH_LfhmvWzER0Cb8AFxvpmUKMTvPU&index=49>), and a car review (<https://www.youtube.com/watch?v=JHINhFPY2Kw&list=PLU8wpH_LfhmvnlVt2P-coFLpax8FrWFMI&index=19>)

6.4 Expected duration of study and start times

The study start time will occur in February 2020, and last for 12 months.

6.5 Text and Flow chart of data linkage process

● Baseline data collected on recruitment:

- Demographic data

- Cancer diagnosis

- Cancer management/treatment plan

- ECOG performance score

- Self-reported version of the LANSS (S-LANSS)

- Referral questionnaire from the Australian English (version 2.0) of the Electronic Persistent Pain Outcomes Collaboration (ePPOC).15 ePPOC is an initiative of the Faculty of Pain Medicine, Australian and New Zealand College of Anaesthetists. It is the standardised national data collection form used to measure treatment outcomes and allow coordinated research activity in pain medicine. The questionnaire is a combination of the modified Brief Pain Inventory scale, Depression Anxiety and Stress Scale, Pain Self-Efficacy Questionnaire, Pain Catastrophising Scale, and the Work Productivity and Activity Impairment Questionnaire. ePPOC is designed to be self-administered or may be completed with the assistance of a researcher

- oMEDD, averaged over the previous week. This study will use the analgesia conversion template published by the Faculty of Pain Medicine, Australian and New Zealand College of Anaesthetists.16

- European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of life Questionnaire (QLQ-C30), 2001 version 3. This is the standardised and validated quality of life 30-item questionnaire for cancer patients in international clinical trials.17

● Acceptability and feasibility endpoint

- questionnaire to be completed after each VR session. The questionnaire will ask about the three most commonly known side-effects of VR use: nausea, dizziness, and eyestrain. Patients will score using a 1-10 Visual Analogue Scale on the presence and severity of any of these side-effects. A free text box will be included for extra information or feedback not captured by the questions.

● Effectiveness endpoints

There will be three effectiveness endpoints, two of which are incorporated as part of the ePPOC follow-up questionnaire:

- Modified brief pain inventory scores, primary pain endpoint

- oMEDD doses, averaged over the previous week, secondary pain endpoint

In addition, the QLQ-C30 score will be used as the primary quality of life endpoint.

The follow up data is collected from the patient when they return for their next chemotherapy/radiotherapy session, or via telephone if their chemotherapy/ radiotherapy sessions have ended. The ePPOC and EORTC QLQ-C30 questionnaires have been reproduced verbatim from pages 17-34 of the case reporting form, divided by follow up timepoints.

Timepoints for follow-up is at 1 month, 3 months, and 6 months after recruitment. A flow diagram of data collection is below.

The Case Reporting Form (CRF) for this study is also attached as an appendix.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Baseline dataset on recruitment** | **After each VR session** | **T1m** | **T3m** | **T6m** |
| **Data collection** | - Demographics  - ECOG  - Referral version of ePPOC  - oMEDD  - QLQ-C30 | Acceptability questionnaire | - Follow up version of ePPOC  - QLQ-C30 | - Follow up version of ePPOC  - QLQ-C30 | - Follow up version of ePPOC  - QLQ-C30 |

● Timing and location of VR intervention

There are 3 modules incorporated into the VR software program. Thus, a total of 3 sessions will be provided to each patient enrolled in the intervention arm. Each session will last for a maximum of 30 minutes, as timed by a researcher. Each VR session will occur in separate clinic contacts.

The VR will be administered to patients in a side room located within the Cancer Centre Wellness unit to provide privacy for the patient, and to avoid disturbance to other patients concurrently onsite for their outpatient visits. The VR session will occur after the patient has seen their oncologist.

● Allocation to intervention and control arms

A computer generated randomised sequence, in blocks of 4, will be created and placed in sequentially numbered opaque envelopes. Each envelope will have a unique alphanumeric code to allow patients to be de-identified. After obtaining fully informed consent, 40 patients will be recruited and allocated to receive VR-pain psychology therapy, or VR-delivered distraction therapy.

6.6 Statistical analyses

Acceptability results will be summated and averaged over all VR sessions, and presented as separate mean/SD or median/range data for the control and interventional groups. Analysis of acceptability will be performed using either t-test or the Mann-Whitney test. Primary statistical analysis of effectiveness endpoints will compare between controls and groups at follow up timepoints, using repeated measures ANOVA. Potential confounders, such as the Pain Catastrophising Score, Depression Anxiety Stress Scale, and the baseline oMEDD, will be analysed using a backwards stepwise regression to determine influences on effectiveness outcomes. The statistician will be blinded to group allocation due to use of de-identified codes for patients.

**7. ETHICAL CONSIDERATIONS**

7.1 Recruitment and selection of participants

Cancer patients booked in for regular outpatient clinic followup by their oncologists in the Liverpool Hospital Cancer Therapy Centre Wellness Unit will be screened for eligibility criteria. Patients may be booked in for ongoing medical oncology and/or radiation oncology visits. Those patients who meet the inclusion criteria without any exclusion criteria will be identified by their oncologist as a potential participant. These patients will then be approached by a researcher while the patient is in the Unit to discuss the research project as described below.

7.2 Informed consent

The researcher will inform potential participants that participation in the study is voluntary. Declining to participate in the study will not affect medical care, including their pain management plan. Participants may also withdraw at any point of the study, without consequence for their medical care. However, data already collected up to the point of withdrawal will be used for analysis as intention to treat.

Use of VR is in addition to their standard medical care from their usual oncologist. Researchers are not the primary physicians or oncologists of the participant, and therefore not involved in their routine pain management.

The use of VR does not affect their cancer management. This study will opportunistically recruit participants while they are scheduled for their ongoing clinic visits. Researchers will move the research trolley (containing the VR equipment) to the Cancer Centre so that patients are not required to move within the Hospital.

Each VR therapy module lasts no longer than 30minutes, and thus the delay from their Cancer Centre visit is minimised and not burdensome.

Participants will be informed that the study is a randomised controlled trial. They may thus either be allocated to the intervention arm and receive the pain psychology therapy, or be allocated to the control arm and receive a passive movie experience. Both will be delivered using VR goggles.

If the patient is agreeable to be a participant, recruitment will occur after written informed consent.

7.3 Confidentiality and Privacy

The hardcopy CRF (see appendix) will have a unique anonymous participant code will be provided for each participant to identify the patient. This code will be kept separate to the CRF with patient identifying material. This is due to the need for followup for the next 6 months. When data is transferred to an electronic format for statistical analysis, only the anonymous code will be used, ensuring that the data is not directly identifiable. Analysis will also be performed by a statistician not involved with data collection.

7.4 Data storage and Record retention

All hardcopy CRF records will be stored in the Anaesthesia Department research office. This office is locked by key and records kept in a locked filing cabinet inside the office. The office itself is inside a swipe card accessible only section of Liverpool Hospital. All electronic copies of study data is kept on the research office desktop computer, which is password protected.

Files will be destroyed by depositing in a security disposal bin or by deletion from the research computer, 15 years after last publication of results.

7.5 Competitive interests

The principal investigator received an external peer reviewed competitive grant from Sony Australia/Tour de Cure Foundation to develop the VR-pain control therapy program. Sony Australia does not have any input in the development of the VR-pain control therapy. VR equipment was bought using internal departmental funds.

7.6 Feasibility

All capital equipment and software required for these studies are available to the researchers to perform the study. The protocol was externally peer reviewed at a research trials meeting of the Department of Medical Oncology, and supported by Professor Paul De Souza, Senior Staff Specialist Medical Oncologist, Liverpool Hospital.

**8. OUTCOMES AND SIGNIFICANCE**

Acceptability outcomes are based on patient reporting of side-effects including nausea, dizziness, and eyestrain from using VR. Effectiveness outcomes include pain scores (Modified brief pain inventory scores) and oMEDD doses at 1 month, 3 months, and 6 months in the VR group versus the control group. Functional and quality of life outcomes will be assessed at the same time frames.

This pilot study will provide initial evidence for feasibility and effectiveness of VR pain psychology therapy in cancer pain management. It will provide data for the design of a multicentre, prospective, superiority, randomised controlled trial.

All studies utilising VR for analgesia to date has used the technology only as a passive (non-interactive), distraction tool with effectiveness limited as a transient episode. This study is novel in custom-designing a pain psychological therapy within VR. The therapy is active (requires patient interactive input) and provides analgesia techniques that patients can continue to use after the VR session is over.

**9. TIMELINES / MILESTONES**

The study is expected to commence recruitment in February 2020. Given the volume of patients admitted to the Liverpool Cancer Centre, we anticipate meeting our sample size target of 40 patients recruited within the first 4 months. With a six month follow up, we anticipate conclusion of data collection by November 2020.

**10. PUBLICATION POLICY**

This study will be published in a peer-reviewed pain or cancer medicine journal.

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