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Feasibility and acceptability of perioperative application of biofeedback-based virtual reality versus active control for pain and anxiety in children and adolescents undergoing surgery: protocol for a pilot randomised controlled trial

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ABSTRACT

Introduction Current clinical applications of virtual reality (VR) provide patients with transient pain relief during acutely painful events by redirecting attention. Biofeedback (BF) is a mind–body therapy that effectively produces sustained pain reduction, but there are obstacles to its routine use. Combined, BF-based VR (VR-BF) may increase accessibility while enhancing the benefits of BF. VR-BF has yet to be employed in perioperative care, and as such, no defined treatment protocol for VR-BF exists. The primary aim of this study is to assess the feasibility of the perioperative use of VR-BF in children and adolescents. The secondary aims are to assess the acceptability of VR-BF and to collect pilot efficacy data.

Methods and analysis This is a single-centre, randomised controlled pilot clinical trial. A total of 70 patients (12–18 years) scheduled for surgery anticipated to cause moderate to severe pain with ≥1 night of hospital admission will be randomised to one of two study arms (VR-BF or control). Participants randomised to VR-BF (n=35) will use the ForeVR VR platform to engage their breathing in gamified VR applications. Participants randomised to control (n=35) will interact with a pain reflection app, *Manage My Pain*. The primary outcome is feasibility of VR-BF use in adolescents undergoing surgery as assessed through recruitment, enrolment, retention and adherence to the protocol. Secondary outcomes are acceptability of VR-BF and pilot efficacy measures, including pain, anxiety and opioid consumption.

Ethics and dissemination The protocol was approved by the Nationwide Children's Hospital Institutional Review Board (IRB #STUDY00002080). Patient recruitment begins in March 2023. Written informed consent is obtained for all participants. All information acquired will be disseminated via scientific meetings and published in peer-reviewed journals. Data will be available per request and results will be posted on ClinicalTrials.gov.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a randomised controlled clinical trial, which provides the best clinical evidence and support for an intervention.
⇒ This is a pilot trial and is not powered to assess efficacy outcomes but rather calculated based on target retention level as a measure of feasibility.
⇒ Patients are not blinded to the intervention they receive; however, they are blinded to the study arms.
⇒ One limitation is the specific patient population being studied—children and adolescents between the ages of 12 and 18 years undergoing surgery expected to cause moderate to severe pain with ≥1 night of hospital admission—which may limit the generalisability of findings.
⇒ Another limitation is the academic, tertiary care, paediatric hospital study setting; thus, results may not be generalisable to other clinical settings.

Trial registration number ClinicalTrials.gov Registry (NCT04943874).

INTRODUCTION

Background and rationale

Children and adolescents are at risk of persistent pain[1–4] and opioid use[5] after surgery. While most paediatric patients fully recover after surgery, about 20% develop chronic postoperative pain and maintain a reduced quality of life due to pain.[1] With respect to opioids, many patients are first introduced to narcotics to treat pain in a medical setting,[6] and the postoperative period is a time of particular risk for opioid exposure.[2 7 8] As little

as 5 days of opioid use can increase the risk of persistent use.[7 9] Despite many attempts at increasing the use of opioid-sparing multimodal analgesia, the percentage of patients experiencing pain after surgery has not changed much in the last 20 years,[10 11] and opioids remain the foundation of postoperative pain management.[12] Alternative non-pharmacological methods are needed to lower the dangers and long-term consequences of chronic pain and opioid consumption.

Biofeedback (BF) is a mind–body therapy that has been shown to produce sustained pain reduction using integrated computerised instruments to provide patients with real-time physiological data.[13–30] BF teaches patients relaxation skills, instructing them to modify certain behavioural responses (eg, slow breathing) to affect physiological changes (eg, heart rate) that lead to reduced pain.[13 31 32] Patients can lower their pain by slowing their breathing to increase heart rate variability (HRV),[33] activating the parasympathetic nervous system and increasing vagal afferent tone.[32 34] However, widespread implementation of BF has not been possible due to lack of engagement, the need for trained providers and being too resource intensive.[13 14 35–38] Although effective non-pharmacological therapies, like BF, exist for managing postoperative pain, there is still a gap in their availability in inpatient and acute settings.

Virtual reality (VR) has been used in many clinical settings, predominantly for short-term pain reduction.[38–47] Distraction-based VR (VR-D) redirects patients' attention during acutely painful procedures to reduce pain.[39–66] Our prior pilot study assessing the impact of VR-D in children,[67] along with other studies using VR in adults,[68 69] found VR-D useful for transient reductions in pain but insufficient for treating sustained pain after surgery. Of note, distraction alone without VR has not been shown to provide significant pain relief,[39 66 70] suggesting that the immersive experience delivered by VR may explain the increased efficacy of VR-D to transiently reduce pain versus distraction alone.[61 71] Using VR to deliver mind–body therapies, like relaxation and slow breathing, may increase patient motivation, engagement and accessibility of BF.[37 72] Combining VR and BF is an innovative approach to address the critical need for effective, non-pharmacological pain treatment in children and adolescents.

BF-based VR (VR-BF) opens the possibility for patients to experience the therapeutic benefits of BF while avoiding the challenges associated with traditional mind–body therapies.[37 64 72 73] We have designed a randomised, blinded clinical trial to assess the feasibility and acceptability of a perioperative VR-BF intervention to reduce pain, anxiety and opioid consumption in children and adolescents undergoing surgery anticipated to cause moderate to severe pain. We hypothesise that the use of VR-BF in this population is both feasible and acceptable.

Objectives

The primary objective of this study is to assess the feasibility of perioperative integration of VR-BF in paediatric patients undergoing surgery anticipated to cause moderate to severe pain, including preoperative education and training with one daily, 10-minute session for 5 days before surgery and postoperative application of 10-minute sessions three times per day for 7 days after surgery. Secondary objectives are to assess the acceptability of VR-BF and to collect pilot efficacy data regarding pain, anxiety and opioid reduction.

METHODS AND ANALYSIS

This is a single-centre, randomised controlled clinical trial with two study arms: VR-BF (intervention, n=35) and *Manage My Pain* (active control, n=35). Patients (12–18 years) scheduled for surgery anticipated to cause moderate to severe pain with ≥1 night of hospital admission will be recruited and enrolled. Patient recruitment begins in March 2023, and we anticipate a total study duration of 2 years. This study protocol complies with the Standard Protocol Items: Recommendations for Interventional Trials Statement[74] and the Consolidated Standard of Reporting Trials Statement (figure 1). The study was registered at ClinicalTrials.gov (NCT04943874) on 17 May 2021.

Study setting

Nationwide Children's Hospital (NCH), a tertiary care, academic, paediatric hospital.

Study design

This is a pilot clinical trial of children and adolescents scheduled to undergo surgery anticipated to cause moderate to severe pain (eg, abdominal, chest, orthopaedic) to assess the feasibility and acceptability of perioperative VR-BF use versus active control. Figure 1 summarises the study design. All participants are managed postoperatively by the Acute Pain Service and receive either VR-BF or control technology in addition to standard care.

Outcome measures

Primary outcome

Our primary outcome is the feasibility of perioperative application of VR-BF and active control in our study population.

Secondary outcomes

Our secondary outcomes are acceptability and preliminary efficacy of VR-BF (reduction in pain intensity, pain unpleasantness and opioid consumption).

Participants

We are recruiting 70 patients (35/group) aged 12–18 years scheduled to undergo surgery anticipated to cause moderate to severe pain with ≥1 night of postoperative hospital admission. Eligibility criteria are as follows:

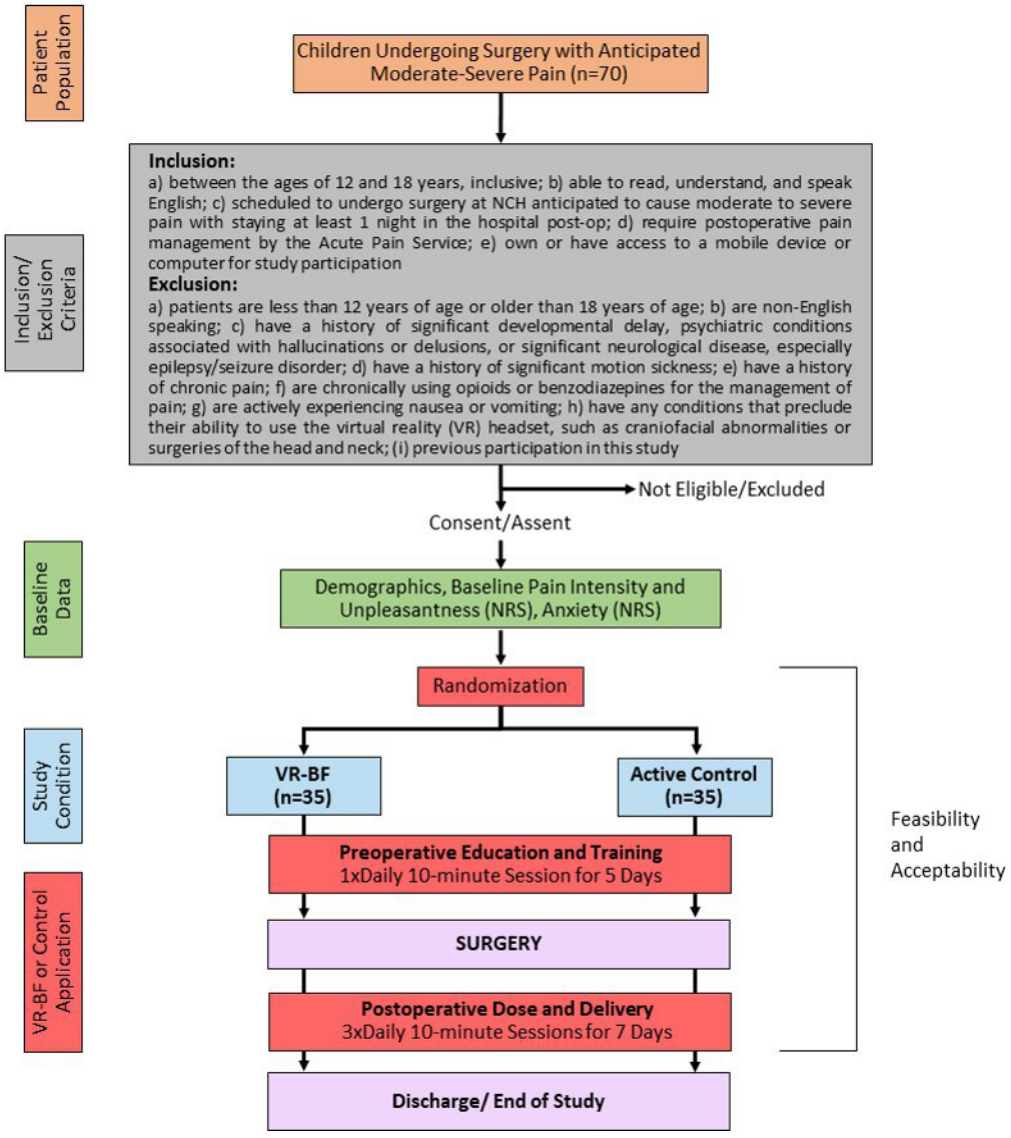

Figure 1 Study flow chart. NCH, Nationwide Children's Hospital; NRS, Numerical Rating Scale; VR-BF, biofeedback-based virtual reality.

Inclusion

(a) 12–18 years old, inclusive; (b) able to read, understand and speak English; (c) scheduled to undergo surgery at NCH anticipated to cause moderate to severe pain with ≥1-night postoperative hospital stay; (d) require postoperative pain management by the Acute Pain Service; and (e) own or have access to a mobile device or computer.

Exclusion

(a) <12 or >18 years old; (b) non-English speaking; (c) history of significant developmental delay, psychiatric conditions associated with hallucinations or delusions, or significant neurological disease, especially epilepsy/seizure disorder; (d) history of significant motion sickness; (e) history of chronic pain; (f) chronically using opioids or benzodiazepines for the management of pain preoperatively; (g) actively experiencing nausea or vomiting; (h) any conditions that preclude their ability to use the VR headset, such as craniofacial abnormalities or surgeries of the head and neck; and (i) previous participation in this study.

Randomisation

Participants are randomly assigned in a 1:1 fashion to receive either VR-BF (intervention) or *Manage My Pain* (active control). An online tool (www.randomizer.org) was used to generate the randomisation scheme to assign participants based on recruitment order. The randomisation scheme is stored in our Research Electronic Data Capture (REDCap) database (https://www.project-redcao.org/), a secured web-based application for building and maintaining databases and surveys.

Blinding

Although patients are not blinded to the intervention they receive, they are blinded with respect to the study arms. The consent describes the study as assessing technology-based interventions for the management of pain without

specific detail as to what each intervention entails. Data collection is blinded by using a study number for each patient. The biostatistician will be blinded to the patient groups during analysis.

Interventions

All participants receive standard education and training on the benefits of mind–body therapy and are instructed to independently complete one daily 10-minute session for 5 days (total of five training sessions) before surgery using the technology-based intervention they were randomised to receive. After surgery, participants complete three daily 10-minute sessions (morning, mid-day, night; each approximately 8 hours apart) for a total of 7 days (total of 21 postoperative sessions). Participants document session usage (date, time, duration) and self-reported pain intensity, pain unpleasantness, and anxiety scores before and after (immediately, 15 min, 30 min) each session using the Numerical Rating Scale (NRS).[75 76] The duration and frequencies of the preoperative and postoperative protocol defined above are based on a standard time for mind–body therapies,[34 77] as well as our unpublished pilot work in phase 1 of this study assessing the optimal dosing of VR-BF.

VR-BF (intervention)

Participants randomised to the VR-BF group will use the ForeVR VR platform that integrates real-time, patient-generated physiological data into a gamified VR world that teaches patients to achieve and maintain target physiological parameters without the need for a trained provider. Participants will use their breathing to progress through a suite of VR games on the Oculus Quest 2 VR headset. Achievement of target physiological parameters prompts positive changes in the VR game, rewarding and motivating patients to continue achieving these target parameters throughout their VR-BF sessions.

Manage My Pain (active control)

Participants randomised to the control group will use the commercially available application, *Manage My Pain* (www.managemypainapp.com). This application is designed to assist patients with recognising and reflecting on their pain by tracking any symptoms, medication consumption and other activities related to the pain they are experiencing. However, this application lacks the fundamental immersive and instantaneous patient feedback elements of VR-BF as well as instruction on behaviour modification techniques.

Patient recruitment

We plan to enrol 70 patients (one to two patients/week). Surgical patients managed by the Acute Pain Service for moderate to severe postoperative pain will be recruited continuously throughout the study until enrolment numbers for each cohort are met. Patient lists provided by the surgical schedulers and operating room schedules will be screened to identify potentially eligible patients based on surgical and age criteria in advance. Eligible patients will be approached and given a brief explanation of the study. Once patients agree to study participation, eligibility criteria will be verified, and appropriate consent and assent will be obtained (online supplemental material 1). Patient health information will be recorded and documented in REDCap. A stipend is given for participation (up to $100 per participant).

Study visits

Up to 2 weeks before surgery, participants receive standard education on the benefits of HRV BF and are given the appropriate study arm training, either virtually (study materials shipped prior to this visit) or in person. Participants undergo an independent daily 10-minute training session and log completion for 5 days prior to surgery, and on the first day of training (preoperative day 1), document baseline pain and anxiety ratings using the NRS.[75 76] Participants are asked to bring all study technology to the hospital on the day of surgery. After surgery, participants undergo three daily 10-minute sessions and log completion, continuing to self-report pain and anxiety ratings before and immediately, 15 min and 30 min after each session, for 7 days. While hospitalised, participants are visited by a clinical research coordinator (CRC) daily or as needed to assist with sessions, log documentation or any issues with the technologies. At the final study visit, a CRC will conduct questionnaires and semistructured interviews soliciting patient and parent qualitative feedback on their experiences.

Data collection

Data collection and storage will be done by a study member who maintains Collaborative Institutional Training Initiative training per NCH Institutional Review Board (IRB) and under the direct supervision of the principal investigator (PI). Data from the electronic health records will be collected onto a standardised case report form and stored in REDCap. Pain (intensity and unpleasantness) and anxiety scores using the NRS[75 76] will be collected from health records and patient logs. Total opioid and benzodiazepine consumption, including any other pain and anxiety medications, will also be collected from health records for each 24-hour period after surgery during hospitalisation and from patient logs following discharge. Opioid medications will be converted to morphine equivalents in mg/kg/day. Sensitivity of physiological parameters (eg, HRV, respiratory rate) to VR-BF usage will be collected from the ForeVR VR platform. Daily reminders via text messages will be sent using the *Scheduled* app (https://scheduledapp.com/).

Measurements

Feasibility is measured by the number of patients who are screened per month, enrolled and randomised to a study arm, successfully complete the last study visit, and adhere to the perioperative use of the intervention or active control. Acceptability is measured by the per cent completion of daily logs, questionnaires and interviews,

Table 1 Feasibility and acceptability outcome measures and benchmarks

	Measures	Definition	Benchmarks	Additional data
Feasibility	Recruitment	Number of patients screened per month	≥80% will meet eligibility criteria	Reasons for not meeting criteria
	Enrolment and randomisation	Number of patients approached who agree to enrol in the study and be randomised to a treatment arm	≥80% of those approached will agree to enrol and be randomised	Reasons for refusal, including unwillingness to be randomised
	Retention	Number of participants who complete the study as defined by participation in the last study visit	≥80% retention	Reasons for dropout
	Adherence	Treatment-specific adherence	≥80% will complete ≥1 session per day for ≥5 days (preop) and ≥3 sessions per day for 7 days (postop)	Reasons for failure
Acceptability	Burden	Per cent completion of daily logs/reports, per cent completion of questionnaires and interview	≥ 80% completion of all study measures	Reasons for failures
	Satisfaction	Patient/parent satisfaction	NA	Questionnaires, semistructured interview
	Credibility	Perception of efficacy	NA	Questionnaires, semistructured interview
	Tolerability	Number and per cent of patients experiencing AEs	<1% will experience a serious AE	Reasons for not tolerating therapy, AEs

AEs, adverse events; NA, not applicable.

patient and parent satisfaction, perception of efficacy and number of patients experiencing adverse events (AEs). Table 1 summarises the measures and targets to assess feasibility and acceptability.

Physiological parameters (eg, HRV, respiratory rate) will be measured by the ForeVR VR platform. Pain intensity, pain unpleasantness and anxiety will be measured using the NRS[75 76] using REDCap surveys sent via text message. Total opioid consumption will be converted to oral morphine equivalents per day adjusted for body weight. Total benzodiazepine and other pain and anxiety medication usage will be collected to assess use of non-opioid analgesics. All medication consumption is measured in mg/kg/day and collected for each 24-hour postoperative period.

Sample size

We will recruit 70 patients for randomisation to one of two study arms (35 per group): intervention and control. The sample size calculation was based on a retention goal of 80%, a measure of feasibility, to estimate a 95% CI with targeted width of 0.22 and an assumed proportion of 80%. We will need a sample size of 70 to ensure that a total of ≥56 patients are included in the final analysis after 80% retention.

Statistical analysis

Due to the nature of this feasibility and acceptability study, no confirmatory hypothesis testing on clinical outcomes collected for exploratory purposes (pain and anxiety ratings, opioid use) will be done. Demographic and baseline characteristics will be summarised for all patients and within each study group (categorical variables using frequency and per cent and continuous variables using mean±SD or median and IQR).

Measures of feasibility and acceptability stratified by study arms will be analysed using descriptive statistics, reporting the rates, variances and two-sided 95% CI. Each CI will be examined to determine if the hypothesised value of 80% is contained within the interval. From the questionnaires and semistructured interviews, we will compile data on satisfaction, credibility, tolerability and additional feasibility data. Participant and family satisfaction of each study arm will be assessed using qualitative feedback from questionnaires and interviews.

Exploratory analysis will be done to assess the impact of VR-BF use on acute postoperative pain, anxiety and opioid consumption. The association between VR-BF dosing and changes to target physiological parameters will be examined to help identify the optimal dose (frequency and duration of use) required to reach consistency in achieving these targets. Any correlation found will be analysed using Spearman or Pearson correlation coefficients between two continuous variables and two sample t-tests or Wilcoxon rank-sum tests, as appropriate, between a continuous and categorical variable. Regression on changes in pain score will be used to examine linear or non-linear correlations between pain reduction and VR-BF use. The same analysis will be repeated for opioid use (mg/kg/day) and patient-reported anxiety scores.

Patient and public involvement

No patients or members of the public were involved in the design, recruitment or conduct of this study. Consideration of the burden and dosing of the intervention was assessed during phase 1 data collection. Information gathered from phase 1 of this pilot study helped guide the development of this clinical trial protocol. Participants may receive information about study results if they wish via a letter describing the results. We will share access to the full protocol to requesting individuals/institutions.

ETHICS AND DISSEMINATION

Ethics

This study is being conducted under the rules and regulations applicable to the conduct of ethical research, and the IRB at NCH has approved this study protocol (IRB #STUDY00002080). This protocol includes clear delineation of the protocol version identifier and date on each protocol amendment submitted to the IRB; clear delineation of plans for data entry, coding, security and storage; clear delineation of mechanisms to ensure patient confidentiality, including how personal information is collected, shared and maintained in order to protect confidentiality before, during and after the trial; statements regarding who has access to data collected during this study; and a model consent form and other related documentation given to participants and/or guardians. We do not anticipate any major protocol modifications during the duration of this study.

Safety

We anticipate that the risk to participants in this study is minimal. The specific VR device is not regulated as a clinical device as it is considered a relaxation device by the Food and Drug Administration. There is minimal or absent risks specific to the VR device, with the greatest risk being motion sickness and/or nausea while the headset is in place.[78] There is a theoretical risk of inducing seizures (0.025% in a paediatric data set supplied by a similar Samsung device). Should motion sickness occur, the participant will be instructed to remove the device. The Oculus Quest and Oculus Quest 2 have been used in prior studies without any reported AEs (CCHMC IRBs #2019-1090, 2020-0258, 2020-0612). We will continue updating to newer versions of the Oculus/Meta Quest as they become available when new equipment is required. To minimise risks, we are excluding patients with a history of seizure disorder or other relevant neurological conditions. AEs are defined in our study as any untoward medical occurrence in a subject during participation in the clinical study or with use of the device being studied which can include a sign, symptom, abnormal assessment or any combination of these regardless of the relationship to study participation. A serious AE (SAE) is an event that meets any one or more of the following criteria: results in death, is life-threatening, results in inpatient hospitalisation or prolongation of existing hospitalisation, or results in persistent or significant disability or incapacity. The researchers shall monitor the patient while the device is applied. SAEs, although unanticipated, will be reported using routine avenues. Weekly laboratory meetings will address the study's quality assurance and safety concerns. Research personnel are instructed to inform the PI immediately of any safety concerns or AEs. The IRB will also be updated when SAEs occur or when mild or moderate AEs determined to result from study participation occur. SAEs that are unanticipated, serious and possibly related to study participation will be reported to the data safety monitoring committee (DSMC), IRB and any other necessary study regulatory committee. We do not anticipate any SAEs that would require stopping this trial early. Therefore, we do not plan to conduct an interim analysis for safety. This consideration will change if SAEs are reported during the study. Although the risk to patients from this clinical trial is low, a DSMC is being used to monitor safety. The DSMC, composed of three experts (clinical research, pain management and digital technology) independent of the protocol, will report to the IRB. The NCH IRB approved this protocol in compliance with existing regulations and policies for the conduct of clinical research.

All patients will receive standard postoperative pain management. Participation and enrolment in this study will not alter their standard of care and will receive the same attention in the postoperative period or during their hospital stay as those non-enrolled patients. Patients are given the opportunity to end participation in the study at any time. Children (12–18 years old) are enrolled in this study, and no other vulnerable populations are included.

Dissemination

Unique data obtained from this research will be widely disseminated through conference presentations at national and international meetings and publications of manuscripts in peer-reviewed journals. Participants may receive trial results if interested. All authors are eligible to participate in dissemination. We do not plan to use professional writers to disseminate study results. Results will be posted on ClinicalTrials.gov.

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