TITLE: Combination of Virtual Reality and Standard of Care Versus Standard of Care Alone for Acute Musculoskeletal Pain Management in Geriatric Emergency Department Patients: A Randomized Clinical Trial

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INTRODUCTION

The proposed **V**irtual **R**eality as an **A**djunct to **P**ain Management for Geriatric Patients in the **ED (VRAP-ED)** project will take place in the Emergency Medicine Department at Maimonides Medical Center. It seeks to enhance the analgesic practices for geriatric patients with acute painful conditions in the emergency setting. Although virtual reality (VR) has demonstrated effectiveness in reducing pain and anxiety in various clinical settings for juveniles and adults[4–6], the analgesic efficacy of VR for geriatric ED patients lacks established data. The project will use a geriatric-focused VR platform.

The project intends to improve pain management for almost 200 geriatric patients by evaluating the effectiveness of virtual reality (VR) in reducing pain and its impact on anxiety & stress reduction. The research project will conduct a randomized clinical trial to investigate the analgesic efficacy and impact on anxiety & stress by using VR as an adjunct to the standard of care (SOC) for pain management in elderly patients presenting to the ED with acute musculoskeletal pain. This will be investigated through a prospective, randomized, non-blinded clinical trial conducted over two years. Eligible patients will be randomly assigned to either the control (SOC) or intervention (SOC+VR) groups. The expected outcomes of this research study will provide insight into the feasibility of using VR in a busy emergency setting for one of the most commonly encountered painful syndromes and to assess the analgesic efficacy as well as the satisfaction of VR application by both patients and ED clinicians.

BACKGROUND AND SIGNIFICANCE

Pain is a significant issue in the elderly population, accounting for a quarter of all pain-related emergency department (ED) visits.1,2 Pain negatively affects the quality of life of geriatric patients, however, effective ED pain management is complicated by comorbidities, polypharmacy, and difficulty in assessing pain, leading to frequent under treatment. By 2030, 20% of Americans will be 65 or older, which will strain the healthcare system with more elderly patients requiring emergency care,3 making this a very important issue.

Pain management is essential in geriatric emergency care as pain is the root cause for up to 75-80% of all presenting chief complaints to the emergency department (ED).9 The ED is uniquely positioned to play an important role in addressing and improving care for the growing share of geriatric patients.

ED providers face numerous challenges when managing pain in elderly patients in a busy emergency setting, often complicated by the presence of age-related physiological changes, multiple comorbid medical conditions, polypharmacy, and declining physical and mental function which makes it difficult to manage pain effectively. 10–13 Moreover, ED providers have varying levels of experience with treating older patients, yielding misconceptions about the level of pain experienced by the elderly and a hesitation to administer analgesics of various classes due to the fear of medications' adverse effects or drug-drug interactions, resulting in inadequate geriatric pain management and suboptimal care.13,14 Despite the high prevalence of pain in the elderly, pain is still often undertreated in this population.11,12,15

Inadequate treatment of elderly pain, in addition to physical suffering, is associated with depression, anxiety, and various degrees of stress.16 Anxiety and stress, as variables itself, are significant issues for geriatric patients as they can increase pain perception/intensity, hinder effective communication about pain with providers, and affect medication efficacy, all of which can potentially impact effective pain management.16–18 Anxiety and stress are prevalent in the elderly population, with studies showing varying rates of each depending on the sample size and demographics. According to a review of studies published in the International Journal of Geriatric Psychiatry, the prevalence of anxiety disorders among older adults ranges from about 4% to 27%.19 Anxiety affects as many as 10-20% of the older population, though it is often undiagnosed. 20 Studies have also found high rates of stress in the elderly population, with some reporting that up to 50% of older adults experience stress.21,22

Numerous ED-based clinical trials demonstrated that older adults are less likely to receive opioid analgesia, either oral or parenteral, both in the ED and upon discharge, when compared to their younger counterparts.23–25 Even with improved pain assessment strategies, only a fraction of elderly patients receive opioid analgesics, and those who receive them are often undertreated based on the dose and frequency.25,26 Similarly, non-opioid analgesics (non-steroidal anti-inflammatory drugs, local anesthetics, anticonvulsants, ketamine) are often contraindicated or poorly tolerated and can be associated with worrisome drug-drug interactions contributing to increased morbidity in the ED.27

While there are harms associated with the use of pain medications in elderly patients, under-treatment of pain in the ED is very problematic and frequently leads to decreased mobility, functional decline, increased dependency on family or care providers, delayed healing, and compromised immune response.12,28,29 Poorly controlled pain is one of the leading predictors of functional decline in older adults. Furthermore, older adults with acute pain are more likely to develop chronic pain further complicating their clinical course and emotional health, resulting in greater healthcare costs.30 Thus, there is a great need for a multi-modal approach to geriatric pain management in the ED with a particular emphasis on non-pharmacologic treatment options used in combination with pharmacologic therapeutics.

Adjunctive non-pharmacologic techniques, such as hypnosis, cognitive behavioral therapy, and music have been used to complement the pharmacological treatment of various types of pain, but the magnitude of these benefits has only been partially embraced by mainstream science.31–34 Physicians are now increasingly investigating complementary and non-traditional ways to manage pain, including the use of virtual reality (VR). VR is a multi-sensory technology that has been used in clinical settings for over 20 years and has been shown to play a role in pain modulation by distraction and by enabling emotional processing, reducing treatment avoidance, and improving pain.35

VR for pain control is an emerging field that is being widely-studied and offers pragmatic use of this advanced technology.5,6,38 Therapeutic VR is an effective, non-pharmacological tool for pain management, with numerous studies documenting its positive effects in reducing stress, anxiety, distress and pain intensity in both juveniles and adults.6,38 Several systematic literature reviews

of randomized controlled studies have found VR to be effective as a complementary form of pain management for acute and chronic pain conditions in both pediatric and adult patients, and has been successfully used in several EDs across the nation for active distraction therapy for medical procedures.4,6,38,39

Currently in geriatric medicine, VR has had broad-spectrum applications focusing primarily on mental health.40 VR has been found to have a strong potential to enhance the physical, emotional, cognitive, and social well-being of older adults. Studies have demonstrated its value as a psychotherapy tool for treating depression and cognitive disorders, and its use is becoming more common in geriatric psychiatry.41,42 However, there is a lack of established literature on using VR technology for pain management in geriatric patients in an emergency setting. Limited and underpowered studies that evaluated an analgesic efficacy of short-term VR therapy in the elderly patients demonstrated a significant pain reduction (25%) for post-surgical and chronic pain.43,44

While overall data is very promising, there is a paucity of evidence supporting the use of immersive VR for acute pain control in the elderly ED patient population.36

The limited evidence supporting VR use in the ED is encouraging, and our project will expand upon current findings by investigating the use of VR therapy in the unexplored geriatric patient population. Our ED will promote VR as a non-pharmacologic analgesic modality to investigate its tolerability and efficacy among older ED pain patients, which can offer a promising new direction for clinical practice and research in this field. This investigation is of vital importance to address geriatric pain management for three key reasons: first, the geriatric population historically presents unique challenges concerning safe and effective ED pain management, second, the changing demographics and increased number of expected geriatric ED visits, and third, adding to the literature of this burgeoning field.

The results of this investigation will impact the field of geriatric pain management. By exploring and investigating this novel approach using VR, this research can form a foundation for non-pharmacological interventions for pain management, leading to new evidence-based modalities that can improve the quality of life, health, and minimize disease and disability for this vulnerable population.

STUDY OBJECTIVES

The main objectives will be measured quantitatively and qualitatively. The primary objective is to measure and compare pain relief for acute musculoskeletal pain conditions using the Numeric Pain Rating Scale (NRS). Secondary objectives include measuring several variables, such as the reduction in anxiety and stress using the modified short State-Trait Anxiety Inventory (STAI) and self-reported stress measures respectively, patient and clinician satisfaction with VR, and overall impression of the subjects' ED pain management and application of VR.

The expected outcomes of this research are to provide insight into the overall feasibility of using VR in a busy emergency care setting, to assess the analgesic efficacy of a VR application, to

evaluate the general acceptance and overall satisfaction of VR by both patients and ED clinicians, and to inform future research in this growing field.

HYPOTHESIS

We hypothesize that VR as an adjunct to SOC will provide better pain relief and reduce anxiety & stress to a greater degree in comparison to SOC alone.

STUDY DESIGN

Subjects: Geriatric patients 65 years of age and older presenting to the ED with a complaint of acute musculoskeletal painful syndrome (traumatic and non-traumatic).

Subjects will have a minimum pain score of 4 or more on a standard 11-point (0 to 10) numeric rating scale (NRS) and will require parenteral analgesia as determined by the treating ED physician. Subjects will be from an all-comers ED population in which all genders, races, identities, religions, etc. will be included.

Eligibility Criteria: Include inclusion and exclusion criteria.

Inclusion Criteria: Patients who are 65 years of age and older who present to the ED with acute traumatic and non-traumatic musculoskeletal painful conditions and have a pain score of 4 or more on the Numeric Rating Scale (NRS) will be deemed eligible. Acute pain will be defined and characterized as sudden, intense, and lasting a short duration, from 1 to 3 months. Patients will warrant parenteral analgesia as per the treating physician's care plan. Patients will have to be awake, alert, and oriented to person, place, and time, and will be able to demonstrate comprehension of the informed consent process and study-related content. Patients will also have to demonstrate the ability to complete assessments, i.e. verbalize the nature of any adverse effects they might experience, as well as express their pain severity by using the NRS, describe their anxiety level via an anxiety inventory scale and self-report the level of stress they feel throughout the study period.

Exclusion Criteria: Subjects will be excluded from the study if they have the following: painful syndrome requiring emergent and/or urgent pain control per the treating physician's directives, pain not consistent with acute pain definition, altered mental status, unstable vital signs (systolic blood pressure <90 or >180 mm Hg, pulse rate <50 or >150 beats/min, and respiration rate <10 or >30 breaths/min), history of recent epilepsy, seizure disorder or vertigo, active headache/nausea/motion sickness/dizziness, being under 65 years of age, and an inability to provide consent (cognitive impairment).

Design**:** Explain if this is a retrospective or prospective study, whether or not it is interventional, involves a drug/biologic/device, etc. Make sure you include information about where study will be run (institution, department, division).

Primary Purpose: Treatment

Interventions:

Type	Name	Description
Device	Virtual Reality Headset	Creates an immersive and engaging virtual experience that can distract the brain from perceiving pain. The engagement platform has been proven in multiple studies to significantly diminish stress, anxiety, depression, and fear contributing to pain and patient distress, potentially decreasing perceived pain intensity.

Intervention Model: Parallel Allocation: Randomized

Subject Participation Duration 2 Hours (120 minutes)

We will conduct a prospective, randomized, non-blinded clinical trial, over a 2-year period, to investigate the efficacy of virtual reality (VR) on pain reduction as a primary outcome (quantitative outcome) and its effect on anxiety and stress (qualitative outcomes) as secondary outcomes in geriatric patients presenting to the ED of Maimonides Medical Center. This clinical trial will focus on patients with complaints of acute traumatic and non-traumatic musculoskeletal pain. These patients will be screened for eligibility and approached by study investigators. Upon meeting the eligibility criteria and completing an informed consent form, patients will be randomized into one of two study groups: 1) Standard of Care or 2) Standard of Care (SOC) plus Virtual Reality. Subjects will include geriatric patients, ages 65 and older, presenting to the ED with acute traumatic and non-traumatic musculoskeletal (MSK) painful syndromes with an initial numeric pain score of 4 and above on a standard 11 point (0 to 10) numeric rating scale (NRS) and requiring analgesia as determined by the treating ED physician. The total sample size for this trial will be 180 subjects (90 per group).

Eligible subjects in the trial will be randomized to either the control group or the intervention group. The control group will receive the standard of care (SOC) analgesia as determined by their treating physician and departmental guidelines. The intervention group will receive VR therapy via a headset as an adjunct to the SOC therapies prescribed. Study investigators will record pain scores, vital signs, and adverse effects at 0, 15, 30, 60, 90, and 120 minutes. In addition, anxiety and stress will be assessed before and after utilization of VR in the intervention group at 0, 30, 60 and 120 minutes. Subjects enrolled in the control group will have an evaluation of anxiety and stress recorded at 0, 30, 60, and 120 minutes as a part of secondary outcome measures as well.

Screening and enrollment: Patients' screening and enrollment will be performed by trained study investigators and research assistants. Subjects will be screened using Allscripts Sunrise ED electronic software through which the electronic medical record (EMR) of the subject will be accessed and study team members will determine eligibility. All patients will be enrolled at various times of the day when study investigators will be available for patient enrollment.

Randomization: Patients will be randomized to either SOC or the VR + SOC group according to a predetermined randomization list, which will be created in SPSS (version 24; IBM Corp, Armonk, NY) with block randomization of every 10 participants. Development of the randomization list,

confirmation of written consent acquisition for all participants, and statistical analyses will be conducted by the Director of Research Administration, who will work independently of any data collection.

Study Intervention/Procedures: After the subject is consented and randomized, the baseline assessments will be completed – study investigators will record pain scores, anxiety scores, stress scores and vital signs. Those who are allocated to the VR study intervention group (SOC + VR) will have the VR device placed on their head and they will engage in an immersive, 10 minutes, VR simulation based on several pre-programmed experiences that will be available on the device's library. The investigators will have access to an iPad/tablet that is linked to the VR headset, to monitor the session and to ensure that the VR device and experience is properly administered and completed.

1. VR Experience and Headset Time Duration for Participants:
   The VR experience will use a geriatric-focused VR platform that has age-appropriate VR content. The VR simulations will consist of pre-loaded, three-dimensional, immersive video content viewed through the VR headset. Participants can choose from a selection of relaxing scenes designed for geriatric patients, such as tranquil nature landscapes or attractive global destinations. By entering stimulating virtual worlds, patients will be surrounded by soothing imagery aimed at decreasing their perception of pain and anxiety. The goal is for participants to feel fully immersed in the tranquil VR environments through the headsets.

The entire duration of the virtual reality (VR) intervention, from the placement to the removal of the headset, is capped at a maximum of 15 minutes. This timeframe encompasses the setup of the VR device with participants and the actual VR simulation, which can last for approximately 5-10 minutes, depending on the nature of the experience. It's worth noting that the VR headsets selected for use are equipped with comfortable silicone/foam face guards and adjustable rubber head straps. These headsets have been successfully employed in our pediatric ED for previous grant projects, with no reported complaints from children, indicating their well-tolerated nature.

Satisfaction Surveys: All subjects regardless of which arm they are randomized to will be given a survey to assess the overall impression of their ED pain management. Subjects randomized to the intervention group (VR+SOC) will be given another survey at the end of the study period (120 minutes) to gauge their satisfaction with VR application. Clinicians will also be given a similar survey to evaluate their satisfaction and general impression of using VR in the ED.

Measuring Pain in Geriatric ED Patients: Pain score will be determined with an 11-point Numeric Rating Scale (NRS) ranging from 0 to 10. We will describe to the patient that "no pain" will be a score of 0 and "the worst pain imaginable" will be scored as a 10. This is the standard scale used for measuring pain.

Measuring Anxiety in Geriatric ED Patients: The level of anxiety in geriatric ED patients will be measured according to the Spielberger State-Trait Anxiety Inventory (STAI-S) scale survey. The STAI survey is a widely used, validated, 20-item survey to measure anxiety in adults and adolescents. For our secondary outcome measure, we will use the 6-item STAI to measure pre and

post intervention (virtual reality) anxiety levels at 0, 30, 60, and 120 minutes. The modified 6-item survey (STAI-6) has been positively validated to the gold-standard 20-item survey that specifically targets degrees of anxiety and is better suited for a fast-paced medical setting such as the emergency department.
Scoring: The STAI score range is between 20 and 80, with scores >40 indicative of appreciable anxiety. To create scores compatible with the original STAI-S scores, the STAI-6 scores will be divided by 6 and multiplied by 20 to give a range from 20-80. With scores >40 indicative of clinical anxiety, the 20-40 range being described as a zero to low level of anxiety, 41-60 as moderate level of anxiety, and 61-80 as high level of anxiety. After a thorough literature review and based on the prior knowledge of the STAI-6 scale, we determined an a priori difference of 3 points on the STAI-6 scale to be statistically significant.

Measuring Stress in Geriatric ED Patients: The level of stress in geriatric ED patients will be measured with an 11-point stress Numerical Rating Scale (SNRS-11) and at a self-reported nominal level. Asking the participants, a variety of questions relating to the stress experienced at set time intervals (0, 30, 60, and 120 minutes) will help us to understand whether the presence and level of stress varies throughout the study period. This secondary outcome measure will be important in elucidating changes in self-reported acute stress responses.

Statistical Design and Power: We are expecting a greater improvement in the mean pain score of the VR group of at least 2.0 points over the standard of care group at 60 minutes (as well as at any other interval postbaseline), with a standard deviation (SD) of 3.0 in both groups. We are also aiming to see simultaneous significance for all three trials using the Bonferroni correction method for an overall alpha of 0.05.

In order to achieve a power of 95% with an overall alpha of 0.05 for this trial, we will require 75 patients per group (150 total). Estimating an approximate 20% dropout/loss to follow up and to account for possible missing data, the total sample size will need to be 180 patients (90 per group). A pre-planned interim data analysis will occur upon reaching a total of 90 patients (45 per group).

Data Collection Procedures: Explain how data will be collected, what data will be collected.

After being evaluated by the treating emergency medicine physician and upon meeting the eligibility criteria, each patient will be approached by a study investigator for the acquisition of written informed consent and Health Insurance Portability and Accountability Act authorization (HIPAA).

Subjects will be consented in accordance to Good Clinical Practice (GCP) without undue influence and coercion. Subjects will then be randomized to either the SOC or VR + SOC group. At baseline, prior to any study-related interventions, study investigators will record pain scores, anxiety scores, self-reported stress measures and vital signs. At subsequent time points, study investigators will record pain scores, vital signs, and adverse effects related to standard of care therapeutics and to the application of VR at 15, 30, 60, 90, and 120 minutes. In addition, name and time of administration of all rescue analgesics will be recorded as well. Anxiety and stress measures will

be recorded at the 0, 30, 60 and 120 minute time points. Patients will be closely monitored for any change in vital signs and for adverse effects during the entire study period (up to 120 minutes) by study investigators.

All data will be recorded on data collection sheets, including patients' sex, demographics, medical history, vital signs and study group allocation by the Project Coordinator, Research Associates, Research Assistants or Co-Investigators. We will also be accessing the participants' EMR after discharge in order to abstract any other relevant data that pertains to the research study. The collected data will be entered into SPSS (version 24.0; IBM Corp) by the Director of Research Administration and Project Director/Senior Research Associate.

Device Sterilization, Maintenance & Storage: In order to adhere to proper sanitation practices, the VR devices will be regularly cleaned and sanitized after each enrolled subject completes their study procedures. Devices will be cleaned using Super Sani-Cloth® disinfectant wipes and further sanitized through the use of a UV light sanitizer box. Devices will be maintained and updated as per the vendor's regularly scheduled maintenance/update plan. All devices will be locked in a secure location at the end of the day and will be charged as needed.

Data Analysis: Explain how data will be analyzed.

Data analyses will include frequency distributions, paired t-test to assess a difference in pain scores within each group, and independent-sample t-test to assess differences in pain scores between the 2 groups at the various intervals. Mixed-model linear regression will be used to compare changes in pain numeric rating scale across the different time points. This will compensate for participants lost to follow-up and allow all patients' data to be analyzed on an intention-to-treat principle.

For categorical outcomes (e.g. complete resolution of pain, stress level, etc.), a Chi-square ($X2$) or Fisher's exact test will be used to compare the primary outcome at 60 minutes as well as the secondary outcomes at all other times points. Percentage differences and 95% confidence intervals between the treatment groups will be calculated for all time points with $p<.05$ to denote statistical significance. Based on the validation of a verbally administered rating scale of acute pain in the ED and the comparison of verbal and visual pain scales, we will use a primary outcome consisting of a minimal clinically meaningful difference of 2.0 between the two groups at the 60-minute pain assessment.

Sample Size: Explain sample size.

We are expecting a greater improvement in the mean pain score of the VR group of at least 2.0 points over the standard of care group at 60 minutes (as well as at any other interval post-baseline), with a standard deviation (SD) of 3.0 in both groups. We are also aiming to see simultaneous significance for all three trials using the Bonferroni correction method for an overall alpha of 0.05.

In order to achieve a power of 95% with an overall alpha of 0.016 we will require 75 patients per group (150 total). Estimating an approximate 20% dropout/loss to follow up and to account for

possible missing data, the total sample size will need to be 180 patients (90 per group). A pre-planned interim data analysis will occur upon reaching a total of 90 patients (45 per group).

Expected Outcomes: Explain what you hope the study will determine.

The primary outcome will include a comparative reduction of pain scores on the NRS between the control (SOC) and intervention group (VR+SOC) at 60 minutes post intervention administration. Secondary outcomes will include anxiety scores and stress levels as well as adverse effects with respect to the VR device, which may include headache and/or dizziness, and SOC therapeutics.

Type	Name	Time Frame	Brief Description
Primary Outcome	Pain Reduction	60 minutes and up to 2 hours	The primary outcome will include a comparative reduction of pain scores on the Numeric Rating Scale (NRS) between the control (SOC) andintervention group (VR+SOC) at 60 minutes post intervention administration.
Secondary Outcome(s)	Anxiety, Stress, and Adverse Effects	Up to 2 hours	Secondary outcomes will include anxiety scores and stress levels as well as adverse effects with respect to the VR experience (may include headache, dizziness, nausea, motion sickness) and SOC therapeutics given.

Adverse Event Reporting (if applicable—drug, biologic, device, intervention): Explain how adverse events, serious adverse events, unexpected reportable events will be monitored and reported. Address whether expected adverse events will be reported.

Clinical studies of prior VR interventions reported few or no side effects in adult and pediatric patients.35,39 Some side effects may include motion sickness, nausea, dizziness or headaches, however, these are rare. Although we do not foresee any serious adverse events (AEs) with VR applications, the study investigators will be with each trial participant throughout the entire study period to monitor for signs of AEs. If any should arise, they will be documented and reported to the principal investigators and the IRB within 24 hours. Periodic data analysis will allow us to assess any other non-serious adverse effects.

The research team, principal investigator/clinical director of research as well as the treating ED physician will be immediately notified if a serious adverse event (SAE) occurs during the study period. The ED team of physicians and nurses will treat the patient appropriately, and subsequently the adverse event report will be submitted to the Institutional Review Board (IRB). Any SAE

requiring intervention will be reported to the IRB within 24 hours of discovery by the research staff. Less serious adverse events will be reported within a week of discovery. There are known expected outcomes and side effects to the procedures, medications, and interventions being received and these are the same risks/side effects as the standard of care – these will be reported if they are serious and require intervention.

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