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Adjunctive virtual reality pain relief after traumatic injury: a proof-of-concept within-person randomized trial

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Abstract

In this study, we hypothesized that immersive virtual reality (VR) environments may reduce pain in patients with acute traumatic injuries, including traumatic brain injuries. We performed a randomized within-subject study in patients hospitalized with acute traumatic injuries, including traumatic brain injury with moderate pain (numeric pain score ≥3 of 10). We compared 3 conditions: (1) an immersive VR environment (VR Blu), (2) a content control with the identical environment delivered through nonimmersive tablet computer (Tablet Blu), and (3) a second control composed of donning VR headgear without content to control for placebo effects and sensory deprivation (VR Blank). We enrolled 60 patients, and 48 patients completed all 3 conditions. Objective and subjective data were analyzed using linear mixed-effects models. Controlling for demographics, baseline pain, and injury severity, we found differences by conditions in relieving pain ($F_{2,75.43} = 3.32$, $P = 0.042$). VR Blu pain reduction was greater than Tablet Blu (-0.92 vs -0.16, $P = 0.043$), but VR Blu pain reduction was similar to VR Blank (-0.92 vs -1.24, $P = 0.241$). VR Blu was perceived as most effective by patients for pain reduction ($F_{2,66.84} = 16.28$, $P < 0.001$), and changes in measures of parasympathetic activity including heart rate variability ($F_{2,55.511} = 7.87$, $P < 0.001$) and pupillary maximum constriction velocity ($F_{2,61.41} = 3.50$, 1-tailed $P = 0.038$) echoed these effects. There were no effects on opioid usage. These findings outlined a potential clinical benefit for mollifying pain related to traumatic injuries.

Keywords: Traumatic brain injury, Trauma, Virtual reality, Pain, Opioids, Heart rate variability

1. Introduction

Virtual Reality (VR) is a technology that intends to create an artificial experience of immersion and presence through head-mounted display and head-tracking presentations of visual and auditory stimuli. During the past decades, there has been an increasing number of experimental studies and clinical trials examining VR as a potential nonpharmacological adjuvant in the medical context including treating both acute and chronic pain.[19,38] Evidence from limited data-based studies have supported that VR shows promise for reducing inpatient pain and mitigating opioid usage.[24,33] However, preliminary studies show that VR might reduce pain or facilitate physical therapy after acute traumatic injuries but are limited by lack of appropriate controls and/or small sample size,[17,26,35] leaving VR efficacy and generalizability remaining uncertain. We are not aware of any study evaluating the use of VR for pain reduction in patients hospitalized with acute traumatic brain injury (TBI), despite a relatively robust literature supporting VR-enhanced rehabilitation for motor and cognitive recovery after admissions for TBI.[2] Given that 2.5 million patients present to emergency departments yearly for TBI and that headache pain from TBI is persistent and associated with chronic opioid use, it is surprising that patients with TBI have not been included in prior studies.[34] To address these gaps, we designed a randomized within-subject study of VR for pain reduction in patients with acute traumatic injuries, including TBI. Moreover, we included 2 active controls to determine how immersive VR would effectively reduce pain in the acute traumatic injury population beyond placebo responses. We hypothesized that VR could reduce pain in the acute inpatient setting after traumatic injury.

2. Methods

2.1. Design

The study design and protocol have been previously published.[10] In brief, we conducted a randomized within-subject crossover clinical trial comparing the effects of an immersive VR environment against 2 control interventions. One control consisted of identical content to the immersive VR environment presented on a nonimmersive electronic tablet to control for immersion effects. The other control consisted of the use of the VR headset without content to control for external sensory deprivation and placebo effects.

The study was conducted from October 2020 to January 2022 in a dedicated trauma hospital. The study was approved by the local institutional review board (Prot. #HP-00090603) and conducted in accordance with the Declaration of Helsinki for human research. All patients provided written and verbal informed consent to participate in the study. The study was also registered at ClinicalTrials.gov (NCT04356963). Data are available by request to the corresponding author.

2.2. Study population

Patients 18 years of age and older with a Glasgow coma scale of 15, hospitalized for a traumatic injury, who reported at least moderate pain (numeric rating scale [NRS] for pain of at least 3 of 10) within 24 hours of enrollment were enrolled in this study. We initially planned to include only TBIs, but we expanded the eligibility to all traumatic injuries because of slow enrollment. Moreover, patients were expected to remain hospitalized for at least 12 hours after enrollment to complete the study protocol. We excluded patients who could not consent for themselves, who had a medical history of seizure or a known intolerance to VR (usually reported as motion sickness), who were pregnant, and who were non-English speaking.

2.3. Protocol

Patients engaged in 3 different 20-minute sessions run by research coordinators and spaced a minimum of 4 hours apart, including (1) a commercially available immersive VR environment, theBlu (WEVR, Inc, Venice, CA) delivered through Oculus Rift (Oculus VR, Irvine, CA) headset, (2) a nonimmersive 2-dimensional mimic delivered through a tablet computer, and (3) a VR control session delivered through a content-less Oculus Rift headset. We refer to those conditions as VR Blu, Tablet Blu, and VR Blank. theBlue scenario, which has been used in previous studies to induce relaxation and a sense of presence, simulates a dynamic encounter with a coral reef surrounded by aquatic wildlife to a soundtrack of calming music.[21] The 3 sessions were run by research coordinators and spaced a minimum of 4 hours apart. The intervention order was counterbalanced using a randomized sequence generator. During the consent process, patients were told that each session was aimed at reducing their pain as follows: "After the questionnaires, you will receive further instructions on how to use the virtual reality or tablet-based system. You will experience 3 sessions aimed at reducing your pain. One session will be a virtual reality-based immersive experience. Another session will be the same as the virtual reality-based experience but presented on a tablet computer instead of the virtual reality headset. In the third session, you will wear the virtual reality headset, but no content will be displayed." We did not specifically ask participants what they did during their time in the VR Blank condition although they were encouraged to close their eyes and relax.

Immediately before and after each session, patients rated their clinical pain intensity through an NRS ranging from 0 (no pain) to 10 (worst possible pain).[20] Headache pain severity specifically was also assessed by the same NRS, which has been previously validated in multiple headache syndromes.[39,42] To assess anxiety, patients completed the 6-item short-form of the Spielberger State-Trait Anxiety Inventory (STAI[22]) before and after each condition.

Potential side effects of VR were measured before and after each session, including neck pain, nausea, dizziness, and light sensitivity according to an NRS ranging from 0 (no symptom) to 10 (worst possible symptom).[27,41] Before and immediately after each session, we also collected vital sign measurements (blood pressure and heart rate) and pupillary maximum constriction velocity. In addition, electrocardiogram (ECG) was recorded 15 minutes before the beginning of each session as baseline and then continuously recorded during the 20 minute-intervention to assess heart rate variabilities relevant to VR-related effects. At the conclusion of all sessions, patients completed a questionnaire regarding their level of engagement and perceptions of effectiveness of each condition to assess patient-oriented outcomes.

The primary treatment team was blinded to the session order and prescribed pain therapeutics independent from the research team. We recorded opioid dosage and administration times.

2.4. Outcomes

The primary outcome was reduction in overall pain severity for VR sessions compared with controls, as measured by the change in the pain NRS rating before vs after each interventional session. Secondary outcomes included changes in headache pain, anxiety, patient-reported engagement, perceived effectiveness, as well as autonomic measurements (ie, pupillary maximum constriction velocity and heart rate variability).

We evaluated opioid consumption as an exploratory outcome because of the complex interactions of patient factors, provider factors, and system factors that drive it.[12,23] We monitored the medication administration record for all opioid usage that we converted to morphine milligram equivalents (MME). Within our trauma units, when opioids are prescribed by convention, they are usually prescribed as needed every 4 hours. We compared the preintervention and postintervention doses of opioids received in morphine equivalents among conditions.

2.5. Autonomic measures

Systolic blood pressure, diastolic blood pressure, and heart rate were assessed before and after each condition by using an automated blood pressure cuff leveled at the right atrium and telemetry, respectively. Heart rate variability was assessed using an ECG recording from standard 5-lead telemetry. Normally distributed R-R intervals provided evidence of good-quality ECG signals, and we used the Z-test to remove segments of low quality (R-R interval outliers). Heart rate variability was obtained following standard measure.[15] We examined both time domain indices including normal-to-normal (NN) mean values and heart rate and frequency domain indices low-frequency (LF) power and high-frequency (HF) power. We split the ECG waveforms of each experiment condition into presession and intrasession periods. A presession period was defined as 25 minutes of recording before the start of an experimental condition, while an intrasession period was the period of the experimental condition from the start time to the end time (approximately 20 minutes). Afterwards, a rolling 5-minute window was applied to both presession and intrasession periods to generate heart rate variability indices, resulting in 4 epochs for each condition. To ensure adequate time for any physiological effects to be realized, we chose the last 3 presession and intrasession epochs for analysis. Time domain heart rate variability indices, NN mean values and heart rate, and frequency indices LF and HF power were extracted using the PhysioNet Cardiovascular Signal Toolbox. Decreasing heart rate variability indices are associated with sympathetic nervous system activity while increasing indices are associated with parasympathetic nervous system activity.

A purer measure of parasympathetic nervous system activity was also obtained by collecting the maximum constriction velocity, as measured by the NPi-200 Pupillometer (NeurOptics, Irvine, CA). The maximum constriction velocity for each pupil is directly reported by the pupillometer. We measured the right eye before and after each condition, given that both eyes constrict in an equal manner.[3] The differences in scores of maximum constriction velocity values before and after each condition were calculated to compare constriction velocity changes among the 3 conditions. Faster maximum constriction velocities represent increased parasympathetic nervous system activity because pupillary constriction occurs independent from sympathetic innervation.[14]

2.6. Side Effects

We accounted for the safety and feasibility of immersive VR for patients with acute traumatic injury including TBI by assessing for changes in neck pain, nausea, dizziness, light sensitivity, and clinical seizures and comparing those changes with those at the baseline and among the 3 conditions.

2.7. Engagement and perceived effectiveness

Immediately after each session, patients completed the Brockmeyer Gaming Engagement Questionnaire, a validated measure of engagement in video game playing that encompasses absorption, flow, presence, and immersion.[4] Patients were instructed to complete the questionnaire based on their engagement in the session that they just completed. At the end of the study, patients rated how effective each condition was in reducing pain on a Likert scale of 0 (not at all effective) to 5 (very effective).

2.8. Statistical analyses

2.8.1. Power calculation and sample size

We enrolled 60 patients, projecting a study dropout of 30%, leaving us with 42 patients to give us an 80% likelihood to detect a treatment difference at a 1-sided 0.05 significance level in our primary analysis of pain reduction.[8,9] Prior work suggests that a 33% pain intensity difference or a 3-point difference on a 0 to 10 pain NRS is an appropriate surrogate for a patient-determined clinically important response.[36]

2.8.2. Missing data

Among the 60 enrolled patients, 1 did not complete any of the 3 experimental conditions, resulting in 59 patients entering the final analysis. The remaining 11 patients who did not finish the whole study but completed at least 1 experimental condition were included in the analysis (**Fig. 1**). Missing data for the primary outcome (pain rating changes) for the 3 experimental conditions ranged between 6.7% (for VR Blu and VR blank) and 8.5% (for Tablet Blu) with the missing data pattern randomly distributed (Little MCAR test: $\chi^2 = 4.72$, $P = 0.581$). To retain most of the study patients in the analysis, we adopted the linear mixed-effects model (LMM) analysis given its superiority in handling missing values.

2.8.3. Primary and secondary analyses

We used descriptive statistics to characterize study patients. Regarding the analyses related to primary and secondary outcomes, we used LMMs to analyze the differences between the ratings over time to allow for missing data expected in a trauma population.[28] For each LMM, we treated the 3 treatment conditions (VR Blu vs Tablet Blu vs VR Blank) as the fixed factors to examine whether the 3 conditions would differ in changes in pain intensity, headache, anxiety, objective autonomic measurement of body response (ie, blood pressure, heart rate, heart rate variability, and pupil maximum constriction velocity), as well as potential side effects. We controlled analyses for experimental sequence, demographic variables such as age, sex, race, clinical variables, baseline pain severity, and injury severity score. Pairwise comparisons were conducted wherever a main effect of the intervention conditions was found.

Regarding heart rate variability, LMMs were built to determine the main effect of the 3 experimental conditions (VR Blu vs Tablet Blu vs VR Blank) on the heart rate variability indices (NN mean values, heartbeat rate, and LF and HF power). For each LMM, experimental conditions were set as the fixed factor. The 3 epochs of each condition were set as repeated measures. We also controlled for baseline level of heart rate variability (ie, presession recordings), age, sex, race, and experimental sequence in the LMMs.

Finally, we compared opioid consumption among the 3 treatment conditions within the VR Blu responders and nonresponders using separate LMMs, respectively. Pair-wise comparisons were applied to a significance of 1-tailed P value of 0.05 because we hypothesized VR Blu condition would result in greater improvement in clinical outcomes when compared with those in the Table Blu and VR Blank conditions based on our previous results.[6] Given the proof-of-concept nature of the study, least significance difference (LSD) adjustment was applied for multiple comparisons. SPSS software, version 27 (IBM, Armonk, NY) was used to perform all the analyses.
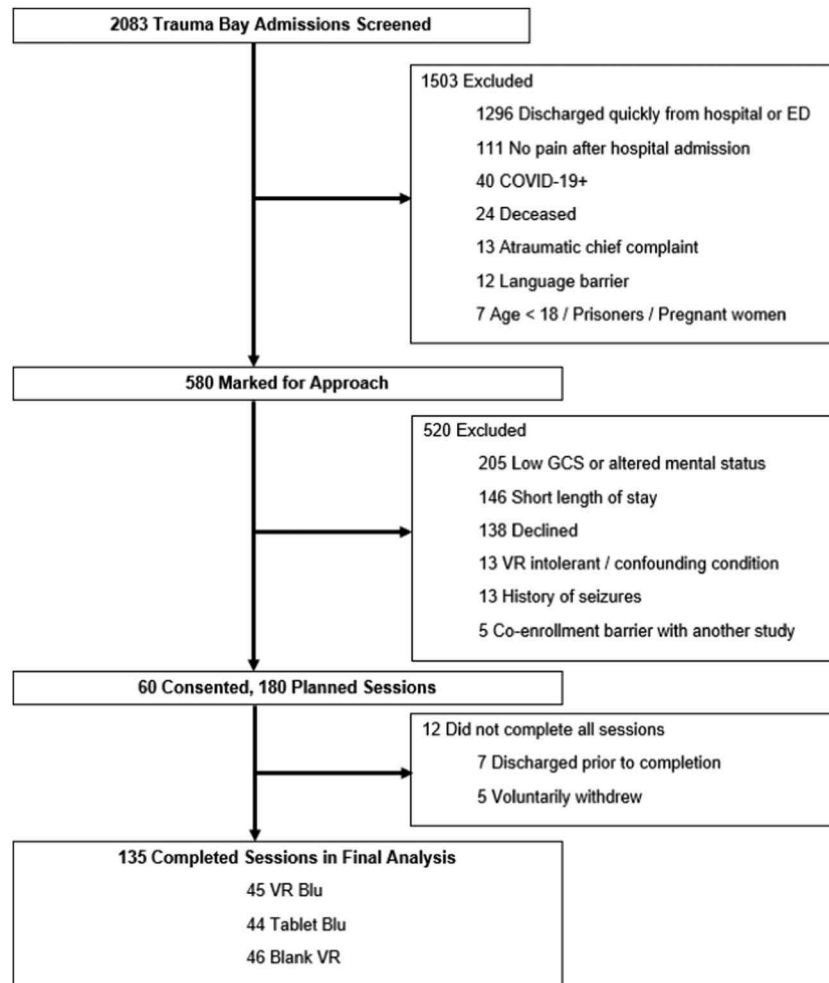
3. Results

We enrolled 60 patients. Seven patients were discharged from the hospital before the completion of the study and 5 patients withdrew from the study because of disinterest without specific complaint, leaving 48 patients who completed the entire protocol (**Fig. 1**). The patients were mostly men (42/60, 70%) with a median age of 53 years interquartile range (IQR), 38-63. One-third (20/60) of the patients had TBIs (**Table 1**). The median baseline pain score was 5.0 (IQR 4.0-7.0).

3.1. Pain reduction

Controlling for the experimental sequence, age, sex, race, baseline pain severity, and injury severity, there was a significant main effect of the experimental conditions on pain intensity ($F_{2,75.43} = 3.32$, $P = 0.042$) (**Fig. 2**). Pair-wise comparisons applying LSD adjustment indicated that pain reduction by VR Blu was significantly greater when compared with that by Tablet Blu (-0.92 vs -0.16, 1-tailed $P = 0.043$), but pain reduction by VR Blu was not different when compared with that by VR Blank (1-tailed $P = 0.243$). Moreover, pain reductions induced by VR Blank (mean $= -1.24$, SEM $= 0.33$) were also significantly greater than those induced by Tablet Blu (mean $= -0.16$, SEM $= 0.29$, LSD-adjusted 1-tailed $P = 0.008$).

VR Blu–induced analgesic effects were then calculated as the continuous delta scores of post-VR minus pre-VR pain intensity ratings. Bivariate correlations indicated no significant relationship between VR Blu–induced analgesic effects and baseline pain intensity (Pearson $r = -0.13$, 1-tailed $P = 0.199$) as well as nonsignificant relationship between VR Blu–induced analgesia and trauma injury severity (Pearson $r = 0.119$, 1-tailed $P = 0.205$).

Figure 1. Enrollment flow chart. After screening 2083 patients admitted to our trauma resuscitation unit, we enrolled 60 patients in the study. GCS, Glasgow Coma Scale; VR, virtual reality.

Age, sex, and race did not influence the results related to pain reductions induced by VR Blu condition, as revealed by nonsignificant multivariate regression controlling for baseline pain and injury severity (age: beta = −0.23, 1-tailed P = 0.111; sex: beta = −0.09, 1-tailed P = 0.299; and White vs non-White race: beta = −0.53, 1-tailed P = 0.300).

3.2. Headache pain reduction

Among patients with TBI, VR Blu did not significantly reduce headache pain more than the other conditions ($F_{1,18.21}$ = 0.051, P = 0.951). Among patients without TBI, VR Blu induced greater reductions in headache pain compared with VR Blank (mean difference = 0.717, 95% CI 0.089-1.344, 1-tailed P = 0.013) but nonsignificant headache reduction compared with Tablet Blu (mean difference = 0.133, 95% CI −0.787 to 1.054, 1-tailed P = 0.386).

3.3. Opioid use

The main effect of the 3 conditions on opioid consumption was not significant ($F_{1,73.89}$ = 0.13, P = 0.876). Fourteen patients (29%) had pain reduced by at least 3 points on the 11-point NRS after VR Blu, defining them as VR Blu responders. Subgroup analyses within VR Blu responders and nonresponders indicated

a marginal significant main effect of the 3 conditions within the VR Blu responders ($F_{2,8.00}$ = 3.88, P = 0.066). That is, VR Blu responders had significant reductions in opioid intake after VR Blu compared with Tablet Blu (LSD-adjusted 1-tailed P = 0.012) but not after VR Blank condition (1-tailed P = 0.063) (**Fig. 3**). No such effects were observed within the VR Blu nonresponders ($F_{2,55.46}$ = 1.58, P = 0.218).

3.4. Anxiety

There was no significant effect of the experimental condition on patient anxiety changes, as measured by the short-form STAI ($F_{1,77.48}$ = 1.66, P = 0.198).

3.5. Autonomic measures

There were no significant effects of condition on changes in systolic blood pressure ($F_{2,61.93}$ = 1.13, P = 0.330) or heart rate ($F_{2,70.22}$ = 1.98, P = 0.146) after controlling for experimental sequence, age, sex, race, baseline pain severity, and injury severity. We observed a significant main effect of the 3 VR conditions on diastolic blood pressure ($F_{2,70.68}$ = 3.38, P = 0.004) where VR Blu induced a significant decrease in diastolic blood pressure when compared with VR Blank condition (LSD-adjusted 1-tailed P = 0.050) but no different from the Tablet Blu (LSD-adjusted 1-tailed P = 0.102).
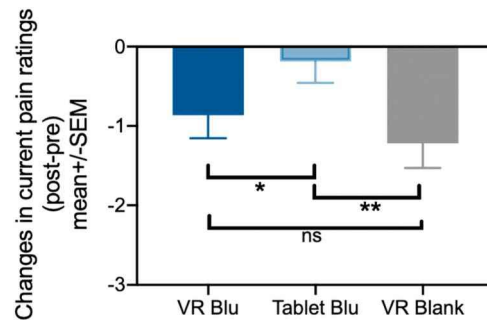
Table 1

Patient characteristics.

Characteristic*	N = 60
Age, median (IQR)	53 (38-63)
Female	18 (30)
Race	
White	37 (61.6)
Black	19 (31.6)
Asian	2 (3.3)
Native Hawaiian/Pacific Islander	1 (1.6)
Other	1 (1.6)
Injury (AIS > 0)	
Head	29 (48)
Head w/traumatic brain injury	20 (33)
Face	20 (33)
Neck	8 (13)
Thoracic	26 (43)
Abdominal	29 (48)
Spine	15 (25)
Upper extremity	28 (42)
Lower extremity	35 (58)
Traumatic brain injury	
Intracranial hemorrhage	13 (65)
Subdural hematoma	10 (50)
Subarachnoid hemorrhage	8 (40)
Epidural hematoma	1 (5)
Cause of injury	
Fall	23 (38)
Motor vehicle collision	17 (28)
Gunshot wound	7 (12)
Stabbing	5 (8)
Motorcycle collision	4 (7)
Pedestrian struck	3 (5)
Assault	1 (2)
Medical history	
Depression	18 (30)
Anxiety	16 (27)
Chronic pain	13 (22)
Alcohol abuse	13 (22)
Positive toxicology screening	32 (53)
Health insurance	
Private	39 (66)
Medicare	16 (26)
Medicaid	5 (8)
Length of stay, median (IQR) days	7 (4-10)

*Data are presented as number (%) unless otherwise specified.
AIS, abbreviated injury scale.

Figure 2. Reduction in pain severity by intervention. Controlling for the experimental sequence, age, sex, race, baseline pain severity, as well as the level of injury severity, there was a significant main effect of the experimental conditions on the current pain intensity changes ($F_{1,75.43} = 3.32$, $P = 0.042$). That is, pain reductions induced by Tablet Blu condition (mean = -0.16, SEM = 0.29) were significantly lower than those induced by VR Blank condition (mean = -1.24, SEM = 0.33, 1-tailed $P = 0.008$) and significantly lower than induced by VR Blu condition (mean = -0.92, SEM = 0.33, 1-tailed $P = 0.043$). VR, virtual reality.
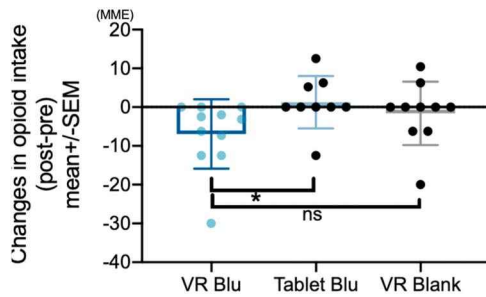
baseline variabilities and controlling for age, sex, race, as well as the sequence of experimental conditions (**Fig. 5A**). No significant differences were observed in heart rate between VR Blu and Tablet Blu (LSD-adjusted 1-tailed $P = 0.316$) or VR Blank and Tablet Blu (LSD-adjusted 1-tailed $P = 0.051$). Moreover, we observed a significant main effect of the experimental condition on the NN mean index ($F_{2,55.511} = 7.87$, $P < 0.001$). Both VR Blu (mean = 874.64 ms, SEM = 15.36 ms) and VR Blank (mean = 867.64 ms, SEM = 10.37 ms) induced greater NN mean increases compared with the Tablet Blu condition (mean = 834.78 ms, SEM = 1.93 ms, 1-tailed $P = 0.008$ and 0.003, respectively), suggesting greater levels of parasympathetic activity induced by both VR conditions (**Fig. 5B**). No main effect of the 3 experimental conditions on frequency domain indices LF power ($F_{2,29.33} = 1.19$, $P = 0.320$) and HF power ($F_{2,57.52} = 0.69$, $P = 0.505$) were found.

3.6. Side Effects

Compared with the baseline and across conditions, there was no significant worsening of neck pain ($F_{2,83.50} = 0.696$, $P = 0.501$), nausea ($F_{2,46.559} = 0.707$, $P = 0.498$), dizziness ($F_{2,89.820} = 0.330$, $P = 0.720$), or light sensitivity ($F_{2,90.602} = 1.330$, $P = 0.270$). The results were unchanged in the subset of patients with TBI. No patients had a seizure or reported motion sickness associated with any interventions.

3.7. Patient engagement and perception

There was a significant main effect of the 3 conditions on Brockmyer Gaming Engagement ($F_{2,76.54} = 20.00$, $P < 0.001$). Pairwise comparison applying LSD adjustment indicated that patients were significantly more engaged in VR Blu than in Tablet Blu or VR Blank (mean 52.31 [SEM 2.04] vs 38.02 [SEM 2.30] vs 35.91 [SEM 2.25], both 1-tailed $P < 0.001$). Engagement was not significantly associated with VR Blu–induced pain relief (Pearson $r = 0.074$, 1-tailed $P = 0.300$), but did correlate with increased pain reduction across all conditions (Pearson $r = 0.15$, 1-tailed $P = 0.029$). There was a significant main effect of the VR conditions on patients' perception of effectiveness ($F_{2,66.84} = 16.28$, $P < 0.001$). Patients perceived VR Blu as more effective than VR

Moreover, decrease in diastolic blood pressure induced by Tablet Blu was significantly greater than that induced by the VR Blank condition (LSD-adjusted 1-tailed $P = 0.012$). In addition, there was a significant main effect of the VR conditions on pupillary maximum constriction velocity ($F_{2,61.41} = 3.50$, $P = 0.038$). Pairwise comparisons indicated that VR Blu increased maximal constriction velocity, a measure of parasympathetic nervous system activity, more than VR Blank (LSD-adjusted 1-tailed $P = 0.006$) but not different than the Tablet Blu (LSD-adjusted 1-tailed $P = 0.059$, **Fig. 4**). Tablet Blu and VR Blank did not significantly differ in maximal constriction velocity (LSD-adjusted 1-tailed $P = 0.081$).

Results from heart rate variability indicated that VR Blu slowed the heart rate ($F_{2,57.31} = 3.61$, $P = 0.033$, mean = 348.82 beats/5 minutes, SEM = 4.23) more than VR Blank did (mean = 361.83 beats/5 minutes, SEM = 3.07, 1-tailed $P = 0.008$), adjusting for

Figure 3. Changes in opioid intake among VR Blu responders by intervention. There were 14 VR Blu responders, defined as patients who had 3 points on greater pain reduction from VR Blu. VR Blu responders had significantly more reductions in opioid intake (measured in morphine equivalents) in the 4 hours after VR Blu compared with Tablet Blu (1-tailed $P < 0.012$) but not after VR Blank condition (1-tailed $P < 0.063$). VR, virtual reality.

Blank (1-tailed $P < 0.001$) and Tablet Blu (1-tailed $P = 0.007$) (**Fig. 6**) in reducing their clinical pain.

4. Discussion

In this randomized within-subject proof-of-concept study of patients hospitalized with acute traumatic injuries, including TBI, we found that adjunctive VR-delivered intervention (VR Blu and VR Blank) surpassed the tablet-delivered benefit in reducing clinical pain, after controlling for demographics, baseline pain severity, and injury severity. No condition had a significant effect on anxiety. VR Blu, but not VR Blank, led to an increase in pupillary maximum constriction velocity and heart rate variability, as measured by NN mean and heart rate, suggesting increased parasympathetic activity induced by VR Blu. While both the VR Blu and the VR Blank conditions decreased pain compared with Tablet Blu, study patients perceived that VR Blu was more effective than Tablet Blu, which they perceived as more effective than VR Blank. Patients who benefited from the VR Blu intervention used less opioids after the intervention than in the hours preceding the VR Blu condition but not after Tablet Blu or VR Blank, suggesting that successful pain reduction with VR may potentially reduce inpatient opioid needs. Regarding safety, we did not find any side effects related to VR in this population such as nausea, photophobia, and dizziness, indicating potential for therapeutic clinical use of VR-delivered interventions.

Our study builds on prior work demonstrating efficacy of VR interventions for acute clinical pain, which has mostly focused on burn and wound care,[30] as well as periprocedural pain.[5] The few studies focused on VR analgesia for acute traumatic pain have been limited by small sample size or lack of controls, limitations shared by studies of VR for other acute pain etiologies.[16,17,26,35] More robust studies of VR for administration of behavioral therapy for chronic pain have led to the US Food and Drug Administration approval for that indication.[7,13] A recent properly powered randomized controlled trial of VR hypnosis for acute traumatic pain, by contrast, found no analgesic benefit.[40]

Our study differs from that study in several important ways. First, we included patients with TBI (compared with only long bone fractures and intra-abdominal injury requiring surgical repair). Second, we used a within-subjects design to increase power. Third, we studied only VR distraction as opposed to VR hypnosis. In addition, we used more modern VR technology, our controls differed, we evaluated pain immediately before and after each session (as opposed to averages over the hospital stay), and as a proof-of-concept study, our analyses were less rigorous in

controlling for multiple comparisons. It is possible that VR analgesia is effective in pain reduction but either it was not administered frequently enough or its effect was not durable enough to affect pain scores averaged over the entire hospitalization in the other trial. Further work is necessary to explore the dosing and durability of VR intervention benefits for acute traumatic pain in inpatients.

Surprisingly, both the VR Blu and VR Blank conditions relieved pain significantly. A recent study found that in healthy controls, more immersive environments increased analgesia in a thermal pain stimulus paradigm.[18] The effect of the presence or engagement on VR-induced pain reduction may be different in trauma inpatients compared with that in healthy controls. The VR Blank per se is not immersive. We did, however, measure engagement, which was significantly higher in the VR Blu condition; engagement was associated with pain reduction, albeit weakly. We posit that VR Blank may have reduced pain intensity through ritual placebo effects by merely wearing the VR headset.[19] In fact, it is possible that both VR conditions benefited from a placebo effect, and future studies should test to what extent there is an effect beyond placebo. An alternative explanation is that wearing the VR headset reduced noxious visual and auditory stimuli from the hospital environment, explaining the pain reduction in both VR Blu and VR Blank compared with the tablet.[29] In the future, a no-intervention intervention would help disentangle placebo vs VR headset–derived benefits. Patients perceived the VR Blu as more effective than the tablet control in line with the results. However, they perceived the VR Blank as inferior, and this may be due to the lack of VR content and therefore engagement. Beyond pain, others have reported effects of interventions on patient-reported measures that are distinct and independent from objective physiological measure.[39]

Nonetheless, we found objective physiological evidence of the effect of the immersive VR intervention on the autonomic nervous system responses. Indeed, VR Blu increased pupillary maximum constriction velocity and heart rate variability, suggesting increased parasympathetic activation.[32] This result echoed those from a previous study where VR induced an increase in parasympathetic nervous system activation that is paralleled with a gain in experimental heat pain tolerance.[6] In fact, the autonomic nervous system may interact with the descending pain modulation pathway, given that brain areas of pain matrix (eg, middle cingulate cortex, anterior cingulate cortex, insular cortex, hypothalamus, amygdala, and periaqueductal gray) also contribute to autonomic responses.[1] It is plausible that VR triggers a rebalancing of sympathetic and parasympathetic nervous system homeostasis that could optimize the endogenous descending pain modulatory system[37] mitigating
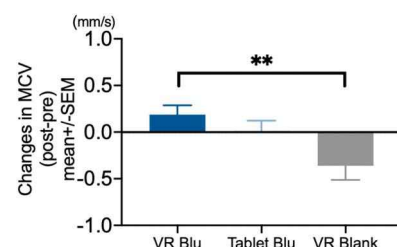
Figure 4. Change in pupillary maximum constriction velocity by intervention. Controlling for the experimental sequences, age, sex, race, baseline pain severity, and injury severity, the main effect of the 3 experimental conditions on maximum constriction velocity was significant ($F_{1,61.41} = 3.50$, $P = 0.038$), whereas VR Blu condition induced a significant greater increase in maximum constriction velocity than the VR Blank condition (1-tailed $P = 0.006$). VR, virtual reality.
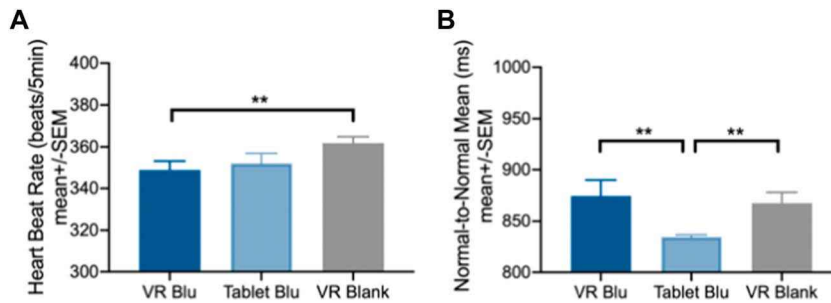
Figure 5. Changes in Heart Rate Variability by Intervention. (A) VR Blu slowed down the heartbeat rate more than VR Blank condition did. (B) Both VR Blue and VR Blank conditions induced greater normal-to-normal mean values compared with Tablet Blu condition. All results adjusted for baseline heartbeat rate and controlled for age, sex, race, and experimental sequences. VR, virtual reality.

pain experience. The immersive VR Blu may affect sensory pathways and ultimately activate parasympathetic responses that decrease pain unpleasantness, while the sensory deprivation of the VR Blank condition may significantly reduce pain but have less effects on the perception of effectiveness.[31] An important aspect of this study is the difference in the results measured by the subjective ratings and the physiological measures. If we would have considered only the subjective measure of pain, VR Blu and VR Blank similar results would have prevented us from understanding part of the observed benefits. Without such measures, we may not have been able to discern meaningful differences between the VR Blu and VR Blank environments. The physiological measures gave an appreciation of the VR Blu condition in line with a previous study[7] where the vagal activation characterized the VR Blu when compared with several control conditions. Our results highlight the importance of incorporating physiologic measures in future studies when testing immersive VR environments. We note that our analysis of physiologic measures did not account for multiple comparisons, warranting cautious interpretation.

Our study has some limitations and strengths. Very few patients with TBI met inclusion criteria. Expected hospital length of stay is usually quite short in mild TBI, and patients with more severe TBI would not be able to engage with the content. Thus, while we initially hoped to enroll only patients with TBI, we opened enrollment to patients with other traumatic injuries and we were underpowered to detect significant effects in the subset of patients with TBI. We did, however, include some patients with (mild) acute TBI, a group in

whom VR has been studied very little. Mild TBI causes headache, light sensitivity, nausea, and dizziness that persists more than 12 months after injury.[25] We were concerned that VR may have carried a risk of exacerbating these symptoms, but it was reassuring that VR Blu did not worsen any of these symptoms compared with the other conditions. Mild TBI may also have an increased risk of seizure but no patient seized because of participating in the study. Early traumatic seizures are unlikely to be photosensitive, and recent expert consensus is that VR technology does not raise seizure concern.[11] Furthermore, we note that there were no safety concerns at all in our entire cohort of inpatients with traumatic injuries. We do not appreciate any compelling reason to exclude patients with traumatic injuries from future trials of VR environments for pain reduction, physical rehabilitation, or other purposes.
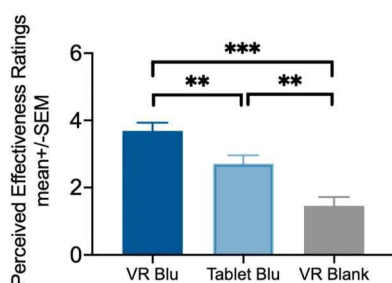
In addition, the intervals between conditions were quite short to improve feasibility of study completion based on brief anticipated length of stay. This limited our ability to evaluate effects on opioid use and the duration of VR intervention effect. This was necessary, however, to include control conditions, which are often lacking from VR studies. Future studies may consider focusing on VR interventions in the outpatient setting to facilitate study of duration of the effect and dosing of VR interventions along with influences on opioid reduction. Finally, the sample size limited our ability to account for multiple comparisons; thus, our findings should be cautiously interpreted.

5. Conclusions

Adjunctive VR interventions to reduce clinical pain in inpatients with acute traumatic injuries, including TBI, are safe and may have modest yet tangible analgesic effects through increased parasympathetic nervous system activation and engagement perceived as beneficial. Future studies of VR in acute traumatic injuries may need to extend to outpatient settings to study long-term effects of VR-based interventions, given generally short hospital lengths of stay.

Figure 6. Perceived Effectiveness of Interventions. Controlling for the experimental sequences, age, sex, race, baseline pain severity, and injury severity, the main effect of the 3 experimental conditions on perceived effectiveness (measured on a Likert scale from 0 (not at all effective) to 5 (very effective)) was significant ($F_{1,65.73} = 16.24$, $P < 0.001$). The self-reported perceived effectiveness in pain reduction was the highest for the VR Blu condition (mean = 3.63, SEM = 0.23) compared with both Tablet Blu (mean = 2.68, SEM = 0.23, $P = 0.005$) and VR Blank conditions (mean = 1.52, SEM = 0.29, $P < 0.001$), where Tablet Blu condition had greater perceived effectiveness than the VR Blank condition ($P = 0.003$). VR, virtual reality.

Conflict of interest statement

L. Colloca received in the past 3 years research grants from the US National Institutes of Health and honoraria for lecturing, payment for expert testimony, consulting fees from Chiesi, Averitas, Shionogi, and Patient-Centered Outcomes Research Institute, and royalties for a didactical book. N. A. Morris has received honoraria for Continuing Medical Education (Grand Rounds, Review Papers, Tweetorials) and serves on the editorial board for *Neurology*. The other authors have no conflicts of interest to report.

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