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Validation of the virtual reality PainCart using diazepam

Submission date 18/10/2023	**Recruitment status** No longer recruiting	[ ] Prospectively registered [ ] Protocol
Registration date 27/11/2023	**Overall study status** Completed	[ ] Statistical analysis plan [ ] Results
Last Edited 09/11/2023	**Condition category** Other	[ ] Individual participant data [ ] Record updated in last year

Plain English summary of protocol

Background and study aims
In a previous pilot study (CHDR2037), the pain and unpleasantness of a nociceptive stimulus were successfully enhanced using virtual reality (VR). During an electrical stimulation test, a wound simulation was presented at the location of the electrodes via VR glasses. When comparing this “enhanced pain” test to a neutral VR pain test (i.e., without wound), healthy volunteers had 1) decreased pain detection thresholds, 2) increased perception of pain intensity, and 3) increased perception of pain unpleasantness. The success of the previous iteration of the VR-PainCart has provided a new paradigm in which novel and promising compounds that augment the affective component of pain can be tested. Further validation of this testing method is therefore necessary to underline its promise for future studies. To assess the sensitivity of the VR PainCart, the affective component of pain will be reduced by the administration of an oral anxiolytic drug. In a previous study, a single dose of diazepam was related to reduced cerebral blood flow to the temporal regions and reduced pain response to a cold pressor test. Additionally, diazepam is known to influence emotional processing and is commonly used to treat clinical anxiety even though the exact mechanism is not yet identified. Diazepam has not yet been used in a study including VR but is very well studied in other contexts and no negative effect is expected on the experience of the simulation (e.g., dizziness, headache) other than a decrease in anxiety. In this study, we aim to include healthy male volunteers between the ages of 18 and 35. To assess the sensitivity of the virtual reality pain test, a single dose of diazepam (5mg) will be used to inhibit the affective pain component.

Who can participate?
Healthy male volunteers aged between 18 and 35 years old

What does the study involve?
This is a randomized single-centre, double-blind, placebo-controlled study to investigate the effect of diazepam on the affective component of pain measured with the VR PainCart. A maximum of 24 healthy subjects will experience three PainCart setups: PainCart without VR (“normal”), VR-neutral and VR+.

What are the possible benefits and risks of participating?
Diazepam is expected to have an analgesic potential. Symptoms such as somnolence, dizziness,

fatigue, reduced vigilance, etc. are to be expected following administration. Subjects should not drive a car and should not engage in activities that require operating vehicles on public roads or dangerous machinery following the administration of diazepam. Thus, the subjects will remain in the clinic under supervision and will be discharged by a physician only if their medical condition allows.

Where is the study run from?
Centre for Human Drug Research (The Netherlands)

When is the study starting and how long is it expected to run for?
June 2023 to November 2023

Who is funding the study?
Centre for Human Drug Research (The Netherlands)

Who is the main contact?
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Contact information

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Public, Scientific

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Additional identifiers

Protocol serial number
CHDR2319

Study information

Scientific Title
Validation of the virtual reality PainCart using diazepam: a randomized single-center, double-blind, placebo-controlled, cross-over study investigating the affective component of pain

Acronym
VR-PainCart

Study objectives
In a previous pilot study (CHDR2037), the pain and unpleasantness of a nociceptive stimulus were successfully enhanced using virtual reality (VR). During an electrical stimulation test, a wound simulation was presented at the location of the electrodes via VR glasses. When comparing this “enhanced pain” test to a neutral VR pain test (i.e., without wound), healthy volunteers had 1) decreased pain detection thresholds, 2) increased perception of pain intensity, and 3) increased perception of pain unpleasantness. The success of the previous iteration of the VR-PainCart has provided a new paradigm in which novel and promising compounds that augment the affective component of pain can be tested. Further validation of this testing method is therefore necessary to underline its promise for future studies. To assess the sensitivity of the VR PainCart, the affective component of pain will be reduced by administration of an oral anxiolytic drug. In a previous study, a single dose of diazepam was related to reduced cerebral blood flow to the temporal regions and reduced pain response to a cold pressor test. Additionally, diazepam is known to influence emotional processing and is commonly used to treat clinical anxiety even though the exact mechanism is not yet identified. Diazepam has not yet been used in a study including VR but is very well studied in other contexts and no negative effect is expected on the experience of the simulation (e.g., dizziness, headache) other than a decrease in anxiety. In this study, we aim to include healthy male volunteers between the age of 18 and 35. To assess the sensitivity of the virtual reality pain test, a single dose of diazepam (5mg) will be used to inhibit the affective pain component.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 01/08/2023, Ethics Assessment Foundation Biomedical Research (BEBO) (Dr. Nassaulaan 10, Assen, 9401 HK, Netherlands; +31 0592 405871; info@stbebo.nl), ref: NL84615.056.23

Primary study design
Interventional

Study design
Randomized single-centre double-blind placebo-controlled study

Study type(s)
Other

Health condition(s) or problem(s) studied
Pain

Interventions
This is a randomized single-centre, double-blind, placebo-controlled study to investigate the effect of diazepam on the affective component of pain measured with the virtual reality (VR) PainCart.

Subjects are randomized in random order by treatment and not in groups. A maximum of 24 healthy subjects will experience three PainCart setups: PainCart without VR (“normal”), VR-neutral and VR+. Before drug or placebo administration, baseline electrical pain detection and tolerance thresholds will be determined with the normal setup. After the baseline measurements, a priming and VR training session is done by VR immersion without actual electrical stimulation or stimulus enhancement. During this session, subjects are introduced to the technology and the simulated environment. After these introductory assessments, the subjects will be given the drug or placebo and follow a pre-set and alternating order of VR PainCart tests. Subjects are at the study location for two full days, both 1 week apart. They have a follow-up done via a phone call. Each subject will receive diazepam or the placebo once per visit.

Intervention Type
Device

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Virtual Reality PainCart

Primary outcome(s)
The following primary outcome measures assess electrical pain perception induced by Virtual Reality PainCart with and without diazepam at each time point of measurement during each treatment period (performed at -2h, 1h, 2h, 3h, 4h, 5h, 6h related to dose with -2h performed as a double baseline):
1. Pain Detection Threshold and Pain Tolerance Threshold measured using an Electrical Stair test
2. Pain (mm), pain intensity (mm), and pain unpleasantness (mm) measured using a Visual Analog Scales (VAS)
3. Pain characteristics measured using the McGill questionnaire

Key secondary outcome(s)
The following secondary outcome measures assess the relationship between the electrical pain perception and personality characteristics at each time point of measurement during each treatment period (performed at -2h, 1h, 2h, 3h, 4h, 5h, 6h related to dose with -2h performed as a double baseline):
1. Pain Detection Threshold and Pain Tolerance Threshold measured using an Electrical Stair test
2. Personality traits measured using all (sub)scales of the Temperament and Character Inventory (TCI)
3. Pain catastrophizing measured using the Pain Catastrophizing Scale (PCS)
4. Pain-related anxiety measured using the Pain Anxiety Symptoms Scale (PASS-20)

The following secondary outcome measures assess the feasibility and potential pharmacological sensitivity of the exploratory biomarkers Grip Effort Task (GET) (performed at -2h, 1h and 7h related to dose) and Facial Emotion Recognition Task (FERT) (performed at -2h, 2h and 7h related to dose):
1. Acceptance rate per effort level
2. Indifference point per effort level
3. Decision time

Completion date
24/11/2023

Eligibility

Key inclusion criteria
1. Signed informed consent prior to any study-mandated procedure
2. Healthy male subjects, 18 to 35 years of age, inclusive at screening
3. Body mass index (BMI) between 18 and 30 kg/m2, inclusive at screening, and with a minimum weight of 50 kg
4. Has the ability to communicate well with the Investigator in the Dutch language and is willing to comply with the study restrictions

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
35 Years

Sex
Male

Key exclusion criteria
1. History of symptoms or any significant including (but not limited to) neurological or psychiatric disorder, if assessed by the Principal Investigator as possibly interfering with the study objectives
2. High pain tolerance (80% or higher value for the pain tolerance of the electrical stair test)
3. Known presence of Virtual Reality Sickness (simulator sickness)
4. All tobacco-containing products must have been stopped 90 days prior to screening
5. Consume, on average, > 8 units/day of (methyl)-xanthines (e.g. coffee, tea, cola, chocolate) or not able to refrain from use during each stay at the CHDR clinic
6. Have a urine drug screen detecting illicit drug of abuse (morphine, benzodiazepines, cocaine,

amphetamine, THC) and/or a positive alcohol breath test
7. Dark skin (Fitzpatrick skin type V - VI), wide-spread acne, tattoos or scarring on the lower limbs. Any deviations from this criterium will be judged and rationalised by the investigator.
8. Evidence of any active or chronic disease or condition that could interfere with, or for which the treatment of might interfere with, the conduct of the study, or that would pose an unacceptable risk to the subject in the opinion of the investigator (following a detailed medical history, physical examination, and vital signs (systolic and diastolic blood pressure, pulse rate, body temperature)). Minor deviations from the normal range may be accepted if judged by the Investigator to have no clinical relevance.
9. Use of any medications (prescription or over-the-counter [OTC]), within 7days of study drug administration, or less than 5 half-lives (whichever is longer). Exceptions will only be made if the investigator documents the rationale
10. Use of any vitamin, mineral, herbal, and dietary supplements within 7 days of study drug administration, or less than 5 half-lives (whichever is longer). Exceptions will only be made if the investigator clearly documents the rationale
11. History of abuse of addictive substances (alcohol, illegal substances) or current use of more than 21 units alcohol per week, drug abuse, or regular user of sedatives, hypnotics, tranquillisers, or any other addictive agent. Exceptions will only be made if the investigator clearly documents the rationale
12. Any known factor, condition, or disease that might interfere with treatment compliance, study conduct or interpretation of the results such as drug or alcohol dependence or psychiatric disease

Date of first enrolment
22/09/2023

Date of final enrolment
31/10/2023

Locations

Countries of recruitment
Netherlands

Study participating centre
Centre for Human Drug Research
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Sponsor information

Organisation
Centre for Human Drug Research

ROR
https://ror.org/044hshx49

Funder(s)

Funder type
Research organisation

Funder Name
Centre for Human Drug Research

Alternative Name(s)
CHDR

Funding Body Type
Private sector organisation

Funding Body Subtype
Research institutes and centers

Location
Netherlands

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date