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The time-related information about a nocebo treatment can modify its onset of action but not the heart rate variability

Submission date
18/09/2020

Recruitment status
No longer recruiting

Registration date
22/09/2020

Overall study status
Completed

Last Edited
19/07/2022

Condition category
Other

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
The nocebo effect plays a crucial role in pain perception. It consists of the worsening of a person' s symptoms (e.g. pain) after receiving an inactive treatment. The nocebo effect is mainly induced by personal expectations about a treatment. Expectation can be modified positively or negatively by the verbal information provided to the person. Studies have shown that telling someone that a hidden inactive treatment will worsen their symptoms will in fact worsen their symptoms. However, it is not known whether time-related information about the onset of action of a nocebo treatment can change its onset of action. Hence, this study aims to find out whether time-related information delivered with a nocebo treatment can change its onset of action.

Who could participate?
Healthy participants aged between 18 and 45

What did the study involve?
The participants are randomly allocated to one of three different groups. The first group are told that the nocebo treatment effect takes place after 5 minutes, the second after 30 minutes, and the third that the treatment is an inactive cream. The nocebo treatment consists of an inactive cream that participants will be told has a hyperalgesic effect (i.e. increases pain). Participants are told to immerse their left hand in circulating cold water (7°C) and resist the pain until it becomes unbearable. The participants perform four of these tests (familiarisation, baseline, after 10 minutes, after 35 minutes) during which their heart rate is measured.

What were the possible benefits and risks of participating?
Participants will not receive any direct benefit from participating in this study, but the findings of this study will provide new evidence on the importance of clinical-patient communication. No risks for the participants are associated with participating in this study.

Where is the study run from?
Vrije Universiteit Brussel (Belgium)

When is the study starting and how long is it expected to run for?
November 2019 to July 2020

Who is funding the study?
1. University of Genoa (Italy)
2. Vrije Universiteit Brussel (Belgium)

Who is the main contact?
Mr Simone Battista
simone.battista@edu.unige.it

Contact information

Type(s)
Scientific

Contact name
Mr Simone Battista

ORCID ID
https://orcid.org/0000-0002-7471-1951

Contact details
Via Magliotto 2
Savona
Italy
17100
+39 (0)19 860250
simone.battista@edu.unige.it

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
NCB-T-01

Study information

Scientific Title
Temporal expectation can modulate the onset of nocebo hyperalgesia but not the heart rate variability: a randomised controlled trial

Study objectives

To test if the manipulation of temporal expectation associated with a nocebo treatment, i.e. an inert cream believed to be hyperalgesic, can modulate nocebo treatment onset of action and its relation to heart rate (HR).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 18/03/2020, Ethics Committee of the Vrije Universiteit Brussel (Commissie Medische Ethiek (O.G. 016) Reflectiegoep Biomedische Ethiek, Laaerbeeklaan 101, 1090 Brussel, Belgium; +32 (0)2 4775584; commissie.ethiek@uzbrussel.be), ref: BUN1432020000002/I/U

Study design
Single-centre randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Nocebo modulation

Interventions
Randomization
1:1 allocation ratio, computer-generated random numbers lists with simple randomisation

In order to test the nocebo temporal onset, participants perform the cold pressor test (CPT), which is an excellent experimental paradigm to induce a type of pain that mimics the effects of chronic conditions. Participants are asked to resist at the CPT as long as they could until the pain became unbearable (VAS = 100). An inactive cream is applied to the participants' dorsal and volar left hand. The cream consists of a water-based gel (KY-gel Johnson & Johnson) which is presented to participants in a transparent plastic tube. Participants believe that the cream is a powerful hyperalgesic. Temporal information provided varies throughout the three groups:

Control: the experimenter explains that the cream is inert, without any effects on pain perception
N5: the experimenter explains that the cream is a powerful hyperalgesic which takes effect after

5 minutes
N30: the experimenter explains that the cream is a powerful hyperalgesic that takes effect after 30 minutes.

After providing written informed consent, participants are seated on a comfortable chair positioned next to the CPT device. The participants perform four CPT tests (familiarisation, baseline, CPT after 10 minutes, CPT after 35 minutes) during which their heart rate is measured.

After providing written informed consent, participants are seated on a comfortable chair positioned next to the CPT device. The experiment starts with a 4-minute heart rate measurement at rest, during which the participant has to breathe naturally and relax. After that, participants are told about the CPT and complete the CPT familiarisation trial. During the CPT, participants have to immerse their left hand in 7 l of circulating cold water (7°C, ± 0.2°C; CPT device: Thermo Scientific model Haake A 10B, Haake SC 100; Thermo Fisher Scientific, Waltham, MA; procedure adapted from Mitchell et al.). To indicate the level to which participants have to lower their hand, the investigator draws a red line from the participant's ulnar to the radial styloid process (wrist level). The CPT is repeated for a total of four times (familiarisation, baseline, Test 10', Test 35') with a break of 20 minutes between each test to restore the baseline hand temperature. Each CPT block starts with 1 minute of HR recording at rest, followed by the actual CPT. Ten seconds before submerging their hands into the CPT device the participants are alerted by the investigator to get ready for the test. Upon a verbal prompt from the investigator ("Go"), the participant lowers their hand into the water, and the investigator starts to record the time between the beginning of exposure and hand withdrawal. Participants are instructed not to move their fingers or hand while they are immersed in the water and to keep their fingers spread with the palm parallel to the bottom of the device, without touching it. The investigator asks and records the participants' pain intensity rate every 15 seconds, through a printed 0-100 Visual Analogue Scale (VAS) that is positioned in front of them. Each participant has to keep their hand in the water basin until the pain in their hand became unbearable (VAS = 100). Once this level of pain is reached, the participant removes their hand from the CPT device and rests it on a towel placed on their knees. The time elapsed between immersion and withdrawal of the hand is recorded as CPT tolerance. At the end of each test 2 minutes of HR are also recorded.

Between the different tests, participants also complete psychological trait questionnaires (see secondary outcome measures).

Intervention Type
Other

Primary outcome measure
The resistance time to the cold pressor test (CPT) measured using a stopwatch at baseline, CPT after 10 minutes, CPT after 35 minutes.
The difference in percentage change of pain tolerance time is calculated as described below:
Δ10 = (CPT Test 10'*100)/Baseline CPT-100
Δ35 = (CPT Test 35'*100)/Baseline CPT-100

Secondary outcome measures
1. Heart rate variability measured using the Polar V800 (Polar Electro Oy, Kempele, Finland) for 4 minutes at the beginning of the trial, 1 minute before each CPT performance and 2 minutes after each CPT performance
2. Level of anxiety measured using the Beck Anxiety Inventory (BAI) between the familiarisation phase with the CPT and the other test sessions

3. Motivational systems measured using the Behavioural Avoidance/Inhibition Scale (BIS/BAS) between the familiarisation phase with the CPT and the other test sessions
4. Fear of pain measured using the Fear of Pain Questionnaire (FAI) between the familiarisation phase with the CPT and the other test sessions
5. Degree of optimism measured using the Revised Life Oriented Test (LOT-R) between the familiarisation phase with the CPT and the other test sessions

Overall study start date
10/11/2019

Completion date
25/07/2020

Eligibility

Key inclusion criteria
1. Healthy volunteers recruited from the student population of the VUB and through different social media outlets
2. Aged between 18 and 45 years old

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
A priori analysis was run with G*Power 3.1 to calculate the sample size needed. Based on Anova for repeated measure test, a sample of 42 participants was determined to accept a power of 80% a significant level of 0.05 and an effect size of 0.41. Assuming a 20% of drop-out rate, 50 participants were necessary to perform the study.

Total final enrolment
51

Key exclusion criteria
Participants that were in cure with antidepressants or anxiolytics, had a history of cardiovascular disease and suffered from psychiatric, neurological, chronic musculoskeletal and pain-related disorders were not considered eligible to participate in the study. Moreover, we instructed the participants not to consume alcohol, caffeine-based drinks or supplements and analgesic medications twelve hours before the experiment.

Date of first enrolment
30/06/2020

Date of final enrolment
25/07/2020

Locations

Countries of recruitment
Belgium

Study participating centre
Vrije Universiteit Brussel
Avenue du Laerbeek 103
Brussel
Belgium
1090

Sponsor information

Organisation
Vrije Universiteit Brussel

Sponsor details
Avenue du Laerbeek 103
Brussels
Belgium
1090
+32 (0)2 4774450
Aldo.Scafoglieri@vub.ac.be

Sponsor type
University/education

Website
http://www.vub.ac.be/en/

ROR
https://ror.org/006e5kg04

Organisation
University of Genoa

Sponsor details
Via Magliotto 2
Savona (SV)

Italy
17100
+39 (0)19 860250
marco.testa@unige.it

Sponsor type
University/education

Website
http://www.unige.it/

ROR
https://ror.org/0107c5v14

Funder(s)

Funder type
University/education

Funder Name
Università degli Studi di Genova

Alternative Name(s)
University of Genoa

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location
Italy

Funder Name
Vrije Universiteit Brussel

Alternative Name(s)
Free University of Brussels, VUB

Funding Body Type
Private sector organisation

Funding Body Subtype
Universities (academic only)

Location
Belgium

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal. At the moment, the statistical analysis and the study design are described in the final version of the manuscript (Material and Methods section) and no other additional documents are intended to be published.

Intention to publish date
31/01/2022

Individual participant data (IPD) sharing plan
According to the responsibilities foreseen by the norms of Good Clinical Practice, the researchers treated the personal data of the participants and the outcomes mentioned in the outcome section, in particular those concerning the name, surname, date of birth, information related to their state of health, their lifestyle and their score at the outcome scales exclusively for this study, as expressed in the Consent Form. To this end, the data mentioned above are collected, processed and stored anonymously by authorised investigators. The data, processed using electronic or electronic means, will be disseminated only in a strictly anonymous form, for example, through scientific publications, statistics and scientific conferences. Participants' data were reported anonymously by identifying each of them with a sequential ID number. The data collected as part of the study are archived in securely locked office drawer units at the Vrije Universiteit Brussel - KIMA department, and will be kept for a minimum period of 5 years to a maximum of 10. The Consent Form was obtained before starting the experiment and after explaining the study in details to the participants and having answered to their possible queries about it. The data process was also explained to each participant.

IPD sharing plan summary
Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		23/03/2022	19/07/2022	Yes	No