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Use of immersive virtual reality for stress reduction during botulinum toxin injection for spasticity (RVTOX): a study protocol of a randomised control trial

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ABSTRACT

Introduction Botulinum toxin injection is a common way to help reduce spasticity in the body caused by central neurological damage such as cerebral stroke, multiple sclerosis or traumatic brain injury. The pain felt during the injection causes most patients to experience significant stress for further injections, the level of which is variable between patients.

Immersive virtual reality is a digital technique that simulates the three-dimensional spatial and sound environment around a person said to be immersed in this virtualised world. The effectiveness of virtual reality comes from the intensity of this multisensory immersion, known as the feeling of presence (ie, subjective experience of being in one place or one environment, even when you are physically in another one).

Only one research article in paediatrics has shown that immersive reality technique has a positive impact on the level of pain and agitation suffered during botulinum toxin injections. The purpose of this study is therefore to evaluate with sufficient assurance the following research hypothesis: virtual reality can help adults cope with the stress and pain of botulinum toxin treatment injection.

Methods and analysis The research hypothesis will be tested using a randomised stepped-wedge method versus a non-invasive technique (headset with virtual reality session) to its control (headset with no image nor audio). The design leads to considering the injection as a statistical unit as all participants will undergo the standard condition, the control technique and virtual reality technique.

Ethics and dissemination Patients will be fully and fairly informed in terms of their understanding of the objectives and constraints of the study and the possible risks involved. They will also be entitled to refuse the study and/or withdraw, and this refusal will have no impact on their follow-up as part of their pathology. Dissemination of the results of this study will be through peer-reviewed publications, and national and international conferences.

Ethics were approved by the Comité de Protection des Personnes Nord-Ouest in January 2022.

Trial registration number NCT05364203.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will be the first to assess the effects of an immersive virtual reality on stress during injections of botulinum toxin in spasticity in adults.
⇒ The tolerance of virtual reality might be different from a patient to another and might be responsible for lost to follow-up, but the number of patients needed to be included was calculated with this possibility.
⇒ The design of this study tends to meet the highest level of evidence.
⇒ Stress is an abstract notion and there are no references for its evaluation, but it will be studied through heart rate variability.
⇒ The effect might be modest for patients who receive injections from many years, due to a habituation effect.

INTRODUCTION

The effectiveness of botulinum toxin injections on spasticity has been widely demonstrated in brain lesions.[1] This treatment is therefore used in many patients with central neurological deficit (stroke, multiple sclerosis, spinal cord injury, traumatic brain injury). Unfortunately, as the effect of botulinum toxin is temporary (approximately 3 months), these intramuscular injections must be repeated every 3–4 months. The tolerance of the injections varies from one patient to another. The pain felt during the injection depends at first on the technique used (electrical stimulation) and the body site where the injection is made (palm and plantar injections are the most painful sites) and secondarily due to the skin break-in.[2] Unfortunately, most patients experience significant stress during the injection.

Concerning botulinum toxin, it has been shown that this toxin, by intramuscular injection, exerts a decrease in hypertonia.[1] In

fact, botulinum toxin has been a reference treatment for focal spasticity since the recommendations of the ANSM (Agence Nationale de Sécurité du Médicament et des produits de Santé) of 2011. One study specifically studied the effect of virtual reality on pain during botulinum toxin injection in paediatrics.[3]

Various reactions of the body caused by stress are known to be related to the change of autonomic nervous system, and stress can be assessed objectively using biomarkers and heart rate variability (HRV).[4] Heart rate can be measured non-invasively, is painless, easy to use and reproducible.[5] It reflects the cardiovascular response to regulatory impulses affecting heart rhythm.[6] In general, HRV is a reliable indicator of autonomic nervous system activity,[7] and many previous studies have used HRV for mental stress estimation.[7–10]

Immersive virtual reality is a digital technique that simulates the three-dimensional spatial and sound environment around a person said to be immersed in this virtualised world. By visually isolating the patient from the medical context, it allows the individual's attention to focus on the virtual experience and be distracted from the unpleasant stimuli of the stressful environment.[11] There is solid evidence from controlled research that virtual reality distraction is effective for reducing experimental pain, as well as the pain associated with burn injury care.[12] One study showed an increase in positive emotions (ie, joy and happiness) and a decrease in anxiety regardless which immersive support methods were offered: participatory virtual reality or contemplative.[13]

Several studies focused on the effectiveness of virtual reality in recent years to reduce pain in various painful medical procedures,[14] reduction of pain in the treatment of burn injuries thanks to a virtual reality system[12 15 16] and pain reduction during episiotomy repair using a virtual reality system.[17] The influence of patients' clinical characteristics on pain during botulinum toxin injections has been studied by Mathevon *et al*.[2] Use of virtual reality in hospitalised patients significantly reduces pain versus a control distraction condition. These results indicate that virtual reality is an effective and safe adjunctive therapy for pain management in the acute inpatient setting.[16]

The only published study on pain felt during botulinum injections concerns the effect of the tracking technique. No studies have yet evaluated the effect of techniques to reduce stress and pain during injection in adults. The only publication concerns the paediatric population and shows decrease of pain and agitation during botulinum injections using virtual reality.[3]

Therefore, the hypothesis of this research is that an immersive virtual reality system can, in adults, reduce the stress and painful experience of botulinum toxin injections. The aim of the study is to evaluate the effect of virtual reality on stress induced by botulinum toxin injections.

METHODS AND ANALYSIS

Trial design

It is a stepped-wedge randomised controlled clinical trial, single blinded as only the investigator will be blinded.

Patients will be randomised into three steps (according to stepped-wedge design), after a first injection in usual condition (in order to measure baseline values, especially for the primary endpoint, HRV): (1) those with a first injection in control condition (virtual reality headset with no image nor audio) and then three injections in virtual reality condition (headset with virtual reality session); (2) those with two first injections in control condition and then two injections in virtual reality condition; and (3) those with three first injections in control condition and then one injection in virtual reality condition.

The design of this trial will adhere to the requirements of the Standard Protocol Items: Recommendations for Interventional Trials (online supplemental material 1). The results will be reported in accordance with the Consolidated Standards of Reporting Trials Statement for non-pharmacological trials.

As each patient will receive five injections, the statistical unit will be the injection. The statistical analysis will be performed by using a random-effects model taking into account between and within-patient variability (patient as random effect). Such design allows to measure the efficacy after several injections, to study the between and within-patient variability and to increase the statistical power. A flow of the participants through the study is provided in table 1.

Participants

We will recruit patients from a cohort of patients treated on a regular basis with botulinum toxin injections in Clermont-Ferrand University Hospital in the Department of Physical Medicine and Rehabilitation. The recruitment will go from 10 May 2022 until 30 October 2024. Patients will have to respond to the inclusion and exclusion criteria listed below (table 2) and give written consent within 1 month after the consultation. The duration of participation in the study is 1 year for each patient.

Table 1 Design of the study

	First injection	Second injection	Third injection	Fourth injection	Fifth injection
Step 1	Standard conditions	Control group	Control group	Control group	Virtual reality
Step 2	Standard conditions	Control group	Control group	Virtual reality	Virtual reality
Step 3	Standard conditions	Control group	Virtual reality	Virtual reality	Virtual reality

Table 2 Eligibility criteria for participants

Inclusion criteria	► Adult, male or female, with spasticity of neurological origin (multiple sclerosis, cerebral stroke, traumatic brain injury, etc) and eligible for botulinum toxin injection ► Able to deliver informed consent to participate in the study ► Affiliation with a social security system
Exclusion criteria	► Medical contraindication to virtual reality (epilepsy, schizophrenia, strabismus, amblyopia, anisometropia), local contraindication of wearing a headset (dermatological lesion of the face or the skull) ► Any medical condition deemed by the investigator to be incompatible with the research (eg, major cognitive disorders MMSE (Mini Mental State Examination <24/30, impaired vision or hearing) ► Indication of sedation by Entonox during botulinum toxin injection sessions ► Every patient who has experienced virtual reality ► Cardiovascular diagnosis of rhythm perturbances or priorly diagnosed anxiety disorders that may hinder results ► Pregnant or breastfeeding women

Interventions

DEEPSEN virtual reality headset will be worn during the entire time of the consultation in front of the eyes, the headphones on the ears. The patient will have to stay on the examination table. Virtual reality scenario is chosen by the patient between eight different scenarios (online supplemental material 2: dunes landscape, mountain during summer or winter, Spitzberg landscape on a boat, mountain picnic in the Alps, countryside in India, canoe and air balloon). The headset can also be controlled by the therapist who can stop at any moment the device, and the device will be disinfected between each participant.

No pain medication in addition to the patient's usual prescription will be allowed during the procedure.

During the injections, the same protocol will be used each time for each patient alone: echo-guided tracking technique or electrostimulation, MYOBOT needle, ice analgesia for palmar or plantar injections.

Primary outcome

The primary outcome is the effect of virtual reality on stress (by HRV)[18 19] at rest, before, during and after botulinum toxin injection. HRV will be evaluated by the fluctuation degree of the duration of heart contractions or the interval between contractions assessed with a heart rate monitor.

Secondary outcomes

One secondary outcome is the effect of virtual reality during botulinum toxin injection on pain induced by the injection. The intensity of pain during botulinum toxin injection will be measured by a simple numerical scale ranging from 0 'no pain' to 10 'worst pain imaginable', immediately after the end of the session.

STATISTICAL CONSIDERATIONS

Sample size estimation

In order to evaluate the effect of virtual reality on stress during botulinum toxin injections, the HRV will be compared between groups, virtual reality versus control group (virtual reality headset without sound and image). Using the log low frequency/high frequency (LF/HF) as primary endpoint, 24 patients will be required to highlight a clinically relevant difference of 0.2 for an SD equals 0.3, a two-sided type 1 error of 5% and a statistical power greater than 80%, according to the results reported by Dutheil *et al*.[18 19]

Due to the design with sequential permutations, 42 patients will be included to take into account between and within-patient variability measured by intraclass correlation coefficient fixed at 0.25. The rate of lost to follow-up should be negligible, as this is a conventional care pathway.

Statistical analysis

All analyses will be performed with the Stata software (V.15, StataCorp, College Station, USA). Continuous variables will be presented as mean and SD or median and IQR. The assumption of normality will be assessed by using the Shapiro-Wilk test. Patients will be described and compared between three steps for the following inclusion variables: eligibility criteria, epidemiological and clinical characteristics. A difference will be determined based on clinical and statistical considerations. The type 1 error will be 5% two sided. A description of the protocol deviations and the causes of lost to follow-up will be carried out.

The primary analysis will be conducted in intention-to-treat sample. A per-protocol analysis will then be conducted.

Primary analysis

The main objective of this study is to assess the effect of virtual reality on stress during botulinum toxin injections. Due to the randomised stepped-wedge design, the primary analysis will be bases on a comparison of the primary endpoint (HRV) between groups (control vs virtual reality) by random-effects model considering between and within-patient and step variabilities (patient and step considered as random effects). The results will be expressed with effect size and 95% CI.

Secondary analysis

In order to assess the effect of repeated use of virtual reality, particular attention will be given to the analysis of group (control vs virtual reality)×injection (second–fifth) interaction evaluated as a fixed effect in the aforementioned mixed models.

The primary analysis will be completed by multivariate analysis (ie, multiple linear regression) to take into account possible confounding factors chosen according to the univariate results and to their clinical relevance (such as age, gender, social economic status, disease duration). The normality of residuals will be studied as aforementioned. If necessary, the dependent variable will be transformed (logarithmic transformation). The results will be expressed with effect sizes and 95% CIs.

Subgroup analysis will be conducted for the primary endpoint to evaluate effect of virtual reality according to age, gender, socioeconomic status and disease duration. The subgroup×group (control vs virtual reality) interaction will be assessed.

Continuous secondary endpoints (pain, heart rate) will be compared between control and virtual reality groups with analogous statistical analysis plan those described for primary endpoint. For categorical endpoints, the comparisons between control and virtual reality groups will be performed with mixed generalised linear regression model. The results will be expressed in terms of absolute differences, ORs and 95% CIs.

The following parameters were collected: root mean square of successive differences between normal, SD of the normal sinus beats, percentage of adjacent NN intervals that differ from each other by more than 50 ms, total power and frequency-domain measurements to separate HRV into its component very low frequency, LF, LF/HF and HF rhythms that operate within different frequency ranges.[20] The relationship between these parameters will be analysed using correlation coefficient (Pearson or Spearman, according to statistical distribution) and applying Sidak's type I error correction for multiple comparisons.

A sensitivity analysis will be conducted to determine the statistical nature of missing data and then to propose the most appropriate method of data imputation (maximum bias or multiple imputation).

Regarding the data from HR monitoring, all devices will be uploaded with Bioharness Zephyr software. Analysis from Zephyr will involve Kubios software. We will delete incorrect data due to artefacts using very low filter in the Kubios software.[20–24]

ETHICS AND DISSEMINATION

Ethics were approved by the Comité de Protection des Personnes Nord-Ouest in January 2022. All participants will receive oral and written information on the aim of the study and the protocol. Written informed consent will be obtained before their inclusion in the study and before performing any specific procedure. During the study, participants will have the opportunity to ask the investigator all questions concerning the protocol. They will be informed that they will be free to stop the study at any time at their own discretion, in accordance with Good Clinical Practice enforced under the French regulatory framework. Any adverse event that could occur during the protocol will be reported to the principal investigator. Should there be any negative impact of participating in the study on the participant's health status, the participant will be entitled to compensation in accordance with the French regulations.

According to the provisions concerning data confidentiality that are available to those responsible for the quality control of biomedical research, all researchers with direct access to the data will take the necessary precautions to ensure the confidentiality of information (participant identification and results). All data collected will be anonymised. Our study will be continued by the investigator and a second article with the results will be published. Dissemination of the results of this study will be through peer-reviewed publications, and national and international conferences.

Patient and public involvement

Patients were not involved in the design and planning of the study. The information will be provided during the previous consultation (at least 1 month before the injection). Patients will be given sufficient time to think about inclusion before giving consent.

DISCUSSION

Both immersion and involvement are necessary for experiencing presence and they interact to determine how much presence is reported.[25] Virtual reality has multiple advantages because it is non-invasive and non-pharmacological, with low cost and easy accessibility and portability. By visually isolating the patient from the medical context, it allows the individual's attention to focus on the virtual experience and be distracted from the unpleasant stimuli of the stressful environment.[11] There is solid evidence from controlled research that virtual reality distraction is effective for reducing experimental pain.[12] Our study aims to assess the effects of an immersive virtual reality on stress during botulinum toxin injections in spasticity in adults. The expected benefit for the patient is improving the tolerance of injections. The same research involved a paediatric population and showed that virtual reality was helpful in reducing botulinum injection-related discomfort in most children.[3]

Although stress is an abstract notion, it can be expressed by HRV, which is sensitive to sympathomimetic influences and requires highly standardised conditions. In general, HRV is a reliable indicator of autonomic nervous system activity,[26] and many previous studies have used HRV for mental stress estimation.[7–9]

Yet, one of the few limitations that might be interesting to cite is first the tolerance of virtual reality. It might be different from a patient to another, and might be responsible for lost to follow-up, for example, due to nausea during viewing. But the number of patients needed to be included was calculated accordingly. Another limitation might be a habituation effect with less stress for patients who receive this therapy since a few years.

Contributors The conception and design of the study were made by MB, IH, BP, MP-V and EC. The drafting of the original protocol was done by MB, IH, BP, MP-V and EC. The coordination of the study was done by IH, MP-V and EC. The acquisition of data was done by MB, IH, BP, MP-V, EC, PG and MB. The design of the statistical analysis plan was done by IH, BP and EC. The drafting of the present manuscript was done by MB, IH, BP, MP-V, CL, EC ans CO. The funding was obtained by AP-P and EC. The final approval was done by MB, IH, BP, MP-V, EC, PG, MB, CL and AP-P.

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Disclaimer The authors are solely responsible for the design and conduct of the study. They are also responsible for all the study analysis, the drafting and editing of manuscript and its final content. The datasets analysed during the current study and statistical code are available from the corresponding author on reasonable request, as is the full protocol.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Obtained.

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