STUDY PROTOCOL 14.05.2025 version 3

Virtuaalitekniikalla ohjatun syvähengityksen ja rentoutumisen harjoittelu lasten ja nuorten hoidossa

– Virtual reality-mediated deep breathing and relaxation training in pediatric care

1. PROJECT SUMMARY

Rationale: the use of virtual reality-based applications can be an effective form of therapy in variety of disorders. Being exposed to a virtual reality environment offers a possibility to experience immersion, which can be used as a tool of controlled exposure or distraction. Combining the immersive virtual nature environment with a traditional mindfulness-based exercise can be an effective method in pain and stress management. Novel non-pharmaceutical treatment options are needed especially for children suffering from anxiety, pain and stress.
Objectives: this is a randomized controlled open clinical study to study the use of the virtual reality environment among child patients. The main goals in this clinical study are to create a virtual reality application for children for learning deep breathing and relaxation and to study their effectiveness, safety and usability in different patient groups and to learn if virtual reality-mediated deep breathing and relaxation training reduce experienced stress and anxiety via autonomic nervous system stimulation.
Methods: this study compares a 6-minute virtual reality-mediated deep breathing or relaxation exercise with the treatment as usual. The exercise is performed using Oculus Quest 2-headset in the hospital setting. Depending on the subgroup of the study population, the exercise is performed either once as a distraction or repeatedly once a week up to four times as a training period. The main outcome is heart rate variability, which is monitored using a Polar H10-heart rate sensor belt. The secondary outcomes are heart rate level, respiratory rate, user feedback, anxiety scale and pain scale.
Population: children aged 8-17 years old.
Time frame: January 2021 – June 2024
Expected outcomes: Our hypothesis is that deep breathing and guided relaxation training will relieve the anxiety patients are experiencing. The immediate effect will be an increased level of heart rate variability and the long-term effect reduction of anxiety symptoms. Furthermore, we hypothesize that patients acquire capability to recognize their autonomic stress reactions and enhance their emotion regulation. We expect the use of the virtual reality solutions to be an effective tool in paediatric treatment.

2. RATIONALE AND BACKGROUND INFORMATION

Virtual reality (VR) techniques have been recently widely used in health care targeting to find novel ways to treat different medical conditions and to prepare patients to unpleasant procedures (Parsons, 2017). The use of VR environments offers a possibility to experience immersion (Riva, Botella, Banos, 2015), which can be used as a tool of controlled exposure or distraction. Recently, VR solutions based on virtual natural environments have been used effectively to induce relaxation, reduce stress and enhance emotion regulation (Pizzoli et al. 2019; Ojala et al. 2019).

According to the review by Maples-Keller et al. (2017), VR therapy solutions can be an effective form of therapy in a variety of mental disorders, including post-traumatic stress disorder (PTSD), social anxiety disorder and generalized anxiety disorder. VR applications have been studied among patients undergoing various unpleasant procedures to evaluate the effect of distraction on experienced pain and anxiety. According to the clinical trial by Chan et al (2019) VR-induced distraction is a safe and effective way to reduce pain during intravenous cannulation or venipuncture. The use of a VR headset was well tolerated and reduced overall fear and pain also among children receiving immunizations (Chad et al, 2018). The advantage of VR applications is that they are cost-effective and well accepted. Most of the youngsters are accustomed to recreative digital applications.

Both somatic pain and psychological distress induce negative emotional reactions and heightened stress. Emotion regulation develops during childhood when parent-child interactions influence the development of children's own emotion regulation neurocircuitry in prefrontal regions, the anterior insula, and the amygdala (e.g. Kerr et al. 2019). The ability to adaptively regulate negative emotion is a protective factor against the development and maintenance of psychopathology (Aldao and Nolen-Hoeksema 2010; Aldao et al. 2010), while difficulties in emotion regulation have been identified as a risk and a maintaining factor particularly for anxiety and depression (e.g. Mennin, McLaughlin and Flanagan 2009).

Functioning of the autonomic nervous system (ANS) has recently been identified as one possible biological system that confers transdiagnostic vulnerability to psychopathology, and high frequency heart rate variability (HF-HRV) has been suggested to function as a transdiagnostic biomarker of self-regulation (Beauchaine and Thayer, 2015). Higher heart rate variability (HRV) has been associated with higher emotional well-being (Beauchaine and Thayer 2015; Kemp and Quintana 2013), with lower anxiety (Chalmers et al. 2014) and better regulated emotional responding (Mather & Thayer 2018).

Impaired autonomic nervous function may be involved also in various functional diseases, such as irritable bowel syndrome (IBS) (Mazurak, 2012). IBS patients have had significantly altered HRV compared to controls, which has suggested decreased vagal influence either due to vagal withdrawal or due to sympathetic dominance in patients (Polster, 2018). Psychological therapies appear to be effective treatments for IBS (Ford, 2019) and tele-hypnotherapy has been shown to reduce pain, anxiety and

IBS severity in patients with IBS (Hasan, 2019). This arouses interest in the possibilities to treat IBS with interventions aiming for regulating the autonomic nervous system.

Deep breathing and relaxation suppress sympathetic action, stimulate parasympathetic action and result in reduction of experienced stress and anxiety, and increased HRV (Goessl, Curtis and Hofmann 2017; Mather and Thayer 2018; Zaccaro et al. 2018). Teaching deep diaphragmatic breathing to children has been used as a behavioral intervention in pediatric practice to help children cope with acute anxiety, stress, and experience of pain (Petersen et al. 2020). Due to their stress and anxiety reducing effects, deep breathing and relaxation exercises could benefit children and adolescents suffering from psychiatric problems or functional diseases like the IBD, or during painful procedures, particularly when integrated with modern technological environments like VR-applications.

The use of VR-applications enables children and adolescents to practice stress and anxiety relieving techniques repeatedly, independently and at various locations, which spares the resources of specialized care and may be significant also for maintaining treatment results. This is of importance, as the number of youngsters in need of specialized care for their anxiety or functional symptoms has been growing.

Enhancing emotion regulation and relieving experienced stress and anxiety using virtual reality mediated breathing and relaxation training could provide new and cost-effective ways of preventing and treating many health problems and disorders in children and adolescents. Stimulating the vagal activity and suppressing sympathetic dominance could reduce subjectively experienced negative emotions and discomfort.

Virtual reality mediated technology could also affect the actual mechanism in the autonomic nervous system that causes symptoms in functional organic and mental diseases, such as in IBS and generalized anxiety disorder.

3. STUDY GOALS AND OBJECTIVES

We will perform a randomized controlled open clinical study to investigate the use of virtual reality environments and applications among pediatric, child psychiatric and adolescent psychiatric patients.

Our aims in this clinical study are:

1. To create virtual reality (VR) applications for children and adolescents for learning deep breathing and relaxation and;
2. To study their effectiveness, safety and usability in different patient groups and;
3. To learn if virtual reality-mediated deep breathing and relaxation training reduces experienced stress and anxiety via autonomic nervous system stimulation.

4. STUDY DESIGN

The study is conducted by Tampere Center for Child, Adolescent, and Maternal Health Research (TamCAM), Tampere, Finland, in close collaboration with the departments of Pediatric unit, Child Psychiatry unit, Adolescent Psychiatry unit and PeeTU (Paediatric Early Phase Clinical Trial Unit) at Tampere University Hospital and TAUCHI research center (Tampere Unit for Computer-Human Interaction) of Tampere University. The clinical study sessions will be performed in the Pediatric and Adolescent Hospital at TAYS Central Hospital, Tampere, Finland.

The research group is also co-operating and consulting with a needle phobia project group working in the pediatric unit in Päijät-Häme Central Hospital, Lahti, Finland.

The clinical study has four different patient groups. The first pilot group consists of children aged 8-12 years having an intravenous catheter placed for treatment or examination purposes. The second and third group consist of children aged 8-12 years and adolescents aged 13-17 years with an anxiety disorder and the fourth group of children aged 8-12 years with irritable bowel syndrome (IBS) or inflammatory bowel disease (IBD).

5. METHODOLGY

5.1. Development of Virtual Reality relaxation application VirNE (Virtual Natural Environments)

TAUCHI Research Center of Tampere University started developing Virtual Reality solution VirNE (Virtual Natural Environments) in the guidance of TamCAM Research Center in summer 2021. VirNE combines a 360-degree nature video with a deep breathing or guided relaxation exercise.

The solution is based on exercise instructions written by Kaija Puura, the professor of Child Psychiatry in Tampere University, Tampere, Finland. The research version of the application is remote-controlled with a computer operated by a research nurse. The virtual reality environment and the relaxation exercises can be presented to the research participants using either a head-mounted display or a projector.

In the first pilot group the exercises are presented via a head-mounted display while the research participant is resting in a hospital bed in a half-sitting position.

The application functionality is ready for all the research phases. It has been tested with voluntary healthy adults and children. However, the development process continues after the first pilot group as we discover the needs for improvement.

5.2. Deep breathing exercise

In the deep breathing exercise, an abstract form expands and shrinks with the rhythm of inhalation and exhalation. The optimal deep breathing rhythm for adults is 6 per

minute, and in the exercise the breathing rhythm is set to 10 breaths per minute for children, and 8 breaths per minute for adolescents. The form is seen on a VR background with a nature scenery with natural sound landscape, and it will gently guide and encourage the patient to keep up with the breathing. The exercise lasts approximately 6 minutes.

5.3. Relaxation exercise

The relaxation exercise uses a virtual natural environment based on looping a relatively short high-quality 360-degree video of a relaxing looking Finnish nature scenery and corresponding surround sound environment. The scenery can be selected by the user from several options, which vary from forest scenery to ocean shore scenery. An animated form is seen on the VR background, and it will gently guide the patient to relax according to the meditation guidance dialog based on breathing and mindfulness exercise.

The script consists of six different phases: introduction to the exercise, setting the body posture, conscious slow breathing, relaxing the body, relaxing the mind, and returning to normal mental state. The exercise lasts approximately 6 minutes.

The script has been initially tested with 20 university students. The experienced anxiety and tension reduced significantly among test subjects as relaxation increased (Jyskä 2020).

5.4. Visual analogue scale for anxiety – scale (The VAS Scale)

The visual analogue scale (The VAS scale) for anxiety is a tool used to assess the intensity of anxiety or pain (Le May et al. 2018). This study uses a digital version of the VAS scale. The virtual form presents a horizontal line marked with scores from 0 to 10 illustrating the level of experienced and self-reported emotions (anxiety, tension and relaxation). The form is to be filled out before and after the intervention.

5.5. The Screen for Child Anxiety Related Emotional Disorders – scale (The SCARED questionnaire)

The SCARED questionnaire is used to screen symptoms linked to anxiety disorders and phobias (Birmaher et al. 1999). The questionnaire comprises 41 claims concerning unpleasant emotions in various everyday life situations. The study patients report whether they relate to the claims constantly, occasionally or never.

5.6. Heart rate variability measurements

The heart rate variability (HRV) will be measured using Polar H10 heart rate sensor belt, which will be placed on the chest of the study patient in the beginning of the

treatment session. The sensor belt will be remotely connected to an Android OS smartphone running Polar Sensor Logger software to follow the current level of the heart rate and to collect the data, which is stored locally in the smartphone before exporting the data.

HRV is measured in three time points referred to as baseline, event and post-event. It allows for investigation of tonic HRV for each of the three measurement points (i.e., baseline, event, post-event). The HRV data is exported to Kubios HRV Scientific analysis software for detailed analysis (Tarvainen et al. 2014). No personal data is collected within the HRV data, and the information collected is stored locally through the study. The data will be deleted after the study.

We will measure the standard deviation of all R–R intervals (SDNN) that reflects all the cyclic components responsible for variability in the period of recording, and the root mean square of successive differences (RMSSD) that reflects vagal tone and is highly correlated with high-frequency (HF) HRV (Laborde, Mosley and Thayer 2017).

5.7. Other measurements

We will monitor the study patients' condition before, during and after the intervention. Blood pressure, heart rate, body temperature and blood oxygen level will be measured before and after the virtual reality training session. Respiratory rate will be monitored by ECG monitoring system continuously during the session. Height and weight will be documented before the intervention as we review study patients' health status by using a structured interview.

6. FOLLOW-UP

There will be no clinical follow-up after the distraction in group 1 or after the training period in groups 2-4. The study patients are encouraged to contact the study group if they have any concerns or questions considering the sessions.

7. DATA MANAGMENT AND STATISTICAL ANALYSIS

7.1. Confidentiality of data and information storage

The collected data will be held safeguarded. Only authorized personnel working in the clinical trial group are allowed to handle the information.

The consent forms and questionnaires will be stored in a locked archive locker in Pediatric and Adolescent Unit in Tampere Central Hospital. The electronic material including HRV data will be banked on the double-secured university server.

To maintain confidentiality, we shall not store any information allowing identifying the subject, keep the research files, forms and consents locked up while unsupervised and protect codes that link patients to the data.

The information register is administered by Tampereen korkeakoulusäätiö sr (Kalevantie 4, 33100 Tampere, Finland). The correspondent person responsible for maintaining the register is Sauli Palmu (+358 503539956, sauli.palmu@tuni.fi).

The storage period of the collected data is 15 years.

7.2. Investigator and site personnel training

All investigators and personnel will be guided to use the virtual reality solutions. The training will be done by written instructions, guidelines and procedure protocols as well as by practical guidance. A logbook monitoring the research personnel training is to be maintained. The persons in charge of training the personnel are Sauli Palmu (study protocol, information security, administration) and Ilmari Jyskä (study devices and software).

7.3. Insurance

All subjects participating the clinical trial are covered by Finnish patient injury insurance.

7.4. Cost of the study

The study costs are covered by grants indicated to the project.

7.5. Payment for participation

No charge may be made on the subjects.

7.6. Return of individual research results

Study patients will not receive individualized feedback or personal analysis from the sessions.

7.7. Sample size determination

The number of the participants is not based on strength calculations, but rather on existing literature on trials and feasibility studies with adults.

7.8. Planned statistical analysis

We will measure the standard deviation of all R-R intervals (SDNN), which reflects all the cyclic components responsible for the variability in the period of recording, and the root mean square of successive differences (RMSSD), which reflects vagal

tone and is highly correlated with high-frequency HRV (HF-HRV). The HRV will be measured in three time points (baseline, event, post-event) allowing the investigation of the changes between these landmarks.

In the study groups 2,3 and 4 the participants and their parents will fill in a questionnaire to measure the anxiety symptoms of the children and adolescents on the first and last week of the study. We will analyze the change in the level of anxiety before and after the training period with repeated measures ANOVA.

8. EXPECTED OUTCOMES OF THE STUDY AND PUBLICATION POLICY

8.1. Expected results and output

Our primary objective is to finish the development process of the virtual reality applications for children and adolescents. We aim for the applications to be straightforward to use and effortlessly available.

We expect to verify the virtual reality solutions are an effective tool for pediatric treatment and training. Concurrently we aim to confirm the applications and devices are safe to use as already indicated in previous clinical studies.

The application used in this study is novel. The user feedback and subjective experiences will help us improve the application as we target it for wide clinical practice.

Our hypothesis is that deep breathing and guided relaxation training will relieve the anxiety patients are experiencing. The immediate effect will be an increased level of heart rate variability and the long-term effect reduction of anxiety symptoms. Furthermore, we hypothesize that patients acquire capability to recognize their autonomic stress reactions and enhance their emotion regulation.

8.2. Publication of results

The results of the study will be released in peer-reviewed international journals as a part of doctoral theses by FM Ilmari Jyskä from the Faculty of Information Technology and Communication Sciences and MD Elina Karppa from the Faculty of Medicine and Health Technology.

9. DURATION OF THE PROJECT

9.1. Timetable

The clinical study group has been established in January 2021. The study has been approved in the Tampere University Hospital Expert Responsibility Area Ethics Committee in June 2021 and in May 2022. Recruiting the study patients started in May 2022 and ended in June 2024.

10. PROBLEMS ANTICIPATED

10.1. Potential risks

There have not been any reported severe adverse effects in clinical studies when exposed to virtual reality environment or when using a virtual reality headset.

It is possible to experience vertigo and nausea resembling motion sickness while observing the 3D scenery with a virtual reality headset. The phenomenon is reversible as the user discontinues using the device.

The use of a virtual reality headset disables viewing the treatment situation normally. It is possible that some patients find this uncomfortable.

10.2. Protection against risks

We will monitor the wellbeing of the subject during the distraction or training. The study patients will receive information on the possible adverse effects prior to the use and will be informed to have a right to discontinue the virtual reality session at any time.

10.3. Adverse event definition

An adverse event is any unpleasant symptom developing or worsening during the clinical trial session regardless of its supposed correlation with the intervention.

10.4. Recording adverse events

The study personnel will monitor all the symptoms subjects are reporting. If any adverse effect is observed, the study session will be ceased, and the symptoms will be described in the follow-up form.

11. PROJECT MANAGEMENT

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12. ETHICS AND INFORMED CONSENT FORMS

12.1. Ethics

Participating in this study is voluntary. The ethics committee has approved the recruitment of minor patients in this study.

13.2 Informed consent forms

We will provide the study patients and their caregivers with sufficient information prior to retrieving the informed consent. The consent form template is available on request.

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