Trial Description

Title

Non-Invasive Vagus Nerve Stimulation for Adolescents with Depression

Trial Acronym

tVNS Youth Depression

URL of the trial

https://www.klinikum.uni-heidelberg.de/Vagusnerv-Stimulation.141505.0.html?&L=0

Brief Summary in Lay Language

Depression is the 2nd leading cause of disability worldwide. About 2.8% of children under the age of 13, and 5.6% of adolescents (13-18 years) fulfill diagnostic criteria for depression. Depression among adolescents is a major risk factor for suicide, which is one of the leading causes of death in this age group. Most importantly, about 40% of children and adolescents with depression do not benefit from the treatment options available (termed: treatment resistant depression). Vagal activity – a psychophysiological marker of emotion regulation – is decreased in children and adolescents with depression, which provides a potential physiological pathomechanism underlying depressive symptomatology. Vagus nerve stimulation (VNS) is effective in the treatment of adults with treatment resistant depression, leading to improved mood and overall wellbeing. Transcutaneous VNS (tVNS) is a new technology, allowing for the non-invasive VNS that is considered safe for the use in children and adolescents. However, proof of concept studies, showing that tVNS alters vagal activity and depressive symptoms by improving mood and emotion regulation in children and adolescents with depression are missing but necessary to transfer tVNS to clinical applications in depressed children and adolescents. Filling this gap is crucial, to offer a treatment option for depressed children and adolescents not responding to existing interventions and thereby reducing the risk of suicide in our youth with treatment resistant depression.

Brief Summary in Scientific Language

An experimental placebo controlled (sham tVNS) design is used. Adolescents perform neuropsychological tasks and provide self-reports of current mood and distress while receiving tVNS or sham (cross-randomized). The study utilizes a within-subject cross-over design. 30 adolescents (14-17 years of age), fulfilling DSM-5 diagnostic criteria for major depression will be enrolled. Adolescents undergo routine diagnostic procedures including assessments of basic sociodemographic characteristics, depressive symptoms and comorbid psychopathology. After physical examination adolescents with severe somatic symptoms will be excluded. Heart rate variability as index of vagal activity will be recorded continuously using electrocardiogram throughout the procedure. Similar, functional near infrared spectroscopy (fNIRS) will monitor oxygenation of the prefrontal cortex as index of cognitive load under task conditions. Primary outcomes are the performance on the Emotional Go/No-Go (emotion regulation)

and Face-Recognition (emotion processing) task and changes in self-reports of mood and distress. The Emotional Go/No-Go task is a computerized task presenting neutral faces or faces of a distinct emotional valence simultaneously with a command of action ("press button"). Participants are trained to inhibit a response (i.e., not to press the button) on certain cue words. Successful inhibition on the task is a well-established measure of emotion regulation, and by evidence impaired in patients with depression. The Face-Recognition task measures the ability to correctly classify emotional expression in the face of others. Depressed patients show difficulties in emotion recognition and tend to classify positive emotions (i.e., joy or happiness) as negative (i.e., fear and anger). Early changes in emotion processing have been shown to predict treatment outcome in clinical studies on pharmacotherapy for depression. Outcomes on both tasks are measures by correct responses (i.e., action or classification) and response time (i.e., in milliseconds). Self-report on positive and negative mood as well as sate-dependent distress will be obtained using visual analogue scales and the Positive and Negative Affect Schedule (PANAS).

Organizational Data

- DRKS-ID: **DRKS00011112**
- Date of Registration in DRKS: **2016/09/29**
- Date of Registration in Partner Registry or other Primary Registry: **[---]***
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **Approved**
- (leading) Ethics Committee Nr.: **S-297/2016 , Ethik-Kommission I der Medizinischen Fakultät Heidelberg**

Secondary IDs

- Universal Trial Number (UTN): **U1111-1188-0829**

Health condition or Problem studied

- ICD10: **F32.1 - Mittelgradige depressive Episode**
- ICD10: **F32.2 - Schwere depressive Episode ohne psychotische Symptome**

Interventions/Observational Groups

- Arm 1: **randomized within subject design; tVNS versus sham stimulation**

  Arm 1: active stimulation of the vagus nerve using a commercial neurostimulation device VITOS (Cerbotec GmBH). Electrical stimulation is applied to the auricular branch of the vagus nerve distributed to the skin of the ear. The duration of stimulation is 35 minutes (15 minutes pre-stimulation period, 20 minutes stimulation while participants perform neuropsychological tasks). The time between the two conditions is 15 minutes.
- Arm 2: **Arm 2: The sham condition is designed as placebo stimulation. Instead of**

stimulating the auricular branch of the vagus nerve, the elctrodes of the neurostimulation device are applied to an outer part of the ear, not innervated by the vagus nerve. Similar to Arm 1 the duration of stimulation is 35 minutes (15 minutes pre-stimulation period, 20 minutes stimulation while participants perform neuropsychological tasks).

Characteristics

- Study Type: **Interventional**
- Study Type Non-Interventional: **[---]***
- Allocation: **Randomized controlled trial**
- Blinding: **[---]***
- Who is blinded: **patient/subject, data analyst**
- Control: **Placebo**
- Purpose: **Basic research/physiological study**
- Assignment: **Crossover**
- Phase: **II-III**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **N/A**

Primary Outcome

The primary end point of the study is the assessment of performance on neuropsychological task on emotion recognition and emotion regulation (correct responses (i.e., action or classification) and response time (i.e., in milliseconds)). Adolescents repeat three neuropsychological task to assess emotion processing and emotion regulation under tVNS and sham. Emotion recognition is measured by the participants' capability to correctly recognize (Test 1) and rate the intensity (Test 2) of key facial expressions using computerized task. The task comprises sets of stimuli that are presented cross-randomized (tVNS vs. sham). Reaction time in milliseconds and correct classifications are measured as outcome. Changes in emotion regulation are assessed using the emotional Go/No-Go paradigm (Test 3). The paradigm involves a continuously presented series of faces of certain emotional valences (e.g., happy, angry) composed of frequent "Go" cues (i.e. angry faces) to which patients respond as rapidly as possible (pressing key on keyboard) and infrequent "No-Go" (i.e., happy faces) cues to which patients do not respond and inhibit their response.

Secondary Outcome

A continous ECG is recorded to quantify changes in heart rate varaibility and functional near infrared spectroscopy (fNIRS) is used to quantify oxygenation of the prefrontal cortex as secondary endpoints of the trial.

Countries of recruitment

- DE **Germany**

Locations of Recruitment

- Medical Center **Klinik für Kinder- und Jugendpsychiatrie, Heidelberg, Heidelberg**

Recruitment

- Planned/Actual: **Actual**
- (Anticipated or Actual) Date of First Enrollment: **2016/12/16**
- Target Sample Size: **30**
- Monocenter/Multicenter trial: **Monocenter trial**
- National/International: **National**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **14 Years**
- Maximum Age: **17 Years**

Additional Inclusion Criteria

1) therapy in our clinic
2) current depressive episode
3) informed consent of study participants and of a parent or a person having parental authority

Exclusion criteria

1) poor knowledge of the German language
2) intake of medicines containing glucocorticoids
3) pregnancy
4) primary neurological or endocrinological disease
5) acute psychotic symptoms
6) acute suicidality
7) any cardiovascular disease

Addresses

- **Primary Sponsor**

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■ **Contact for Scientific Queries**

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Sources of Monetary or Material Support

- **Private sponsorship (foundations, study societies, etc.)**

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- **Private sponsorship (foundations, study societies, etc.)**

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URL: **[---]***

Status

- Recruitment Status: **Recruiting complete, follow-up complete**
- Study Closing (LPLV): **2018/10/16**

Trial Publications, Results and other documents

- Approval of ethics comm. (mandatory for transfer to Studybox) **IRB Approval**
- trial protocol (mandatory for transfer to Studybox) **IRB Study Protocol**

** This entry means the parameter is not applicable or has not been set.*

**** This entry means that data is not displayed due to insufficient data privacy clearing.*