The antidepressive effect of low frequency rTMS as addon to ECT. A pilot study

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Introduction

rTMS (repetitive transcranial magnetic stimulation) is a potential new

noninvasive antidepressant method, which implies non-convulsive focal stimulation of the brain through a time varying magnetic field. rTMS is based on the principle of electromagnetism. An electromagnetic coil placed on the scalp produces an oscillating magnetic field that penetrates the scalp and skull unattenuated and gives rise to a current in the adjacent parts of the cerebral cortex as well as functionally connected centers of the brain. Previous research indicates that the antidepressant effect of rTMS is associated with specific stimulation of the dorsolateral prefrontal cortex. The stimulus frequency has been shown to play a key role in the mechanisms of action of rTMS. Preclinical studies have revealed that low frequency rTMS is associated with long-term inhibition of neuronal activity (long-term depression), while high frequency stimulation is followed by prolonged activation (long-term potentiation). To some extent, this differential effect of the two types of frequencies are reflected in human studies.

The majority of clinically controlled studies on the antidepressant efficacy of rTMS have used high frequency stimulation of left prefrontal cortex supporting the evidence of the antidepressant efficacy of this treatment model, which has been approved by the FDA in USA and later in the EU for the treatment of depression . Fewer studies have used right prefrontal low frequency rTMS, though this model of stimulation obviously has fewer side effects, such as local discomfort and a lower risk of releasing epileptic seizures, than high frequency stimulation . Both stimulus models have been shown to have a statistically and clinically significant antidepressant effect of equal magnitude as add-on to other antidepressant treatments including ECT.

ECT is used in approximately 5% of all psychiatric patients in Denmark with slightly increasing frequency of 11% since 1999. ECT acts through epileptic seizures and have a documented anti-kindling effect involving limbic and paralimbic structures. This kindling repressing effect is probably of significance for the mechanism of ECT. rTMS does not work by inducing seizures, but like ECT low frequency rTMS has been shown to inhibit amygdala-kindled seizures in animal studies. Therefore, theoretically it is possible that low frequency rTMS can amplify the antidepressant effect of ECT.

The present study will be carried out to investigate in which degree right prefrontal low frequency rTMS administered as add-on may accelerate the

antidepressant effect of ECT and thus minimize the side-effects of this treatment.

Material and methods

Design

The present study will be carried out as a randomized, clinically controlled, double blind investigation comparing conventional ECT + sham-stimulation with ECT + right prefrontal low frequency rTMS. Previous research concerning the antidepressant effect of ECT versus rTMS has found remission rates on ECT between 50 and 60%. On the basis of these figures and the outcome of previous RCT studies on the antidepressant effect of low frequency rTMS compared to placebo the difference in the incidence of remission was expected to be 20-30%. A rate difference of 20% would require 81 patients, while a rate difference of 30% would require 31 patients in each group to have 80% power in a 2-sided test at a 5% significance level.

Randomization

The patients are randomly allocated to ECT + rTMS or ECT + sham
According to the principle of block randomization. Six blocks are created with 10 sealed opaque envelopes in each, half of them containing a treatment code for rTMS and the other half for ECT. The envelopes in each block are shuffled thoroughly and numbered from one to 10. To ensure allocation concealment, the patients were randomly allocated to treatment by an independent third part.

Ethics

The study meet the criteria of the Helsinki Declaration II. The patients' consent is based on written and oral information, and the regional ethics committee approved the project protocol.

Study Population

The study population covers inpatients with depression from the County of

Aarhus. The patients are admitted to the department for Depression and Anxiety, Aarhus University Hospital, Risskov, Denmark, and recruited primarily from the city of Aarhus with associated rural districts, a catchment area of approximately 300,000 inhabitants.

Inclusion criteria:

Age between 18 and 80 years and a total score on 17-item HAM-D (24) of 20 or higher and/or 9 or higher on the subscale.

All patients fulfill the ICD-10 criteria for moderate to severe depression and the Diagnostic and Statistical Manual of Mental Disorders-IV criteria for major depressive disorder. Unipolar as well as bipolar patients are included.

Exclusion criteria:

Patients with organic brain damage, personal or family history of epileptic seizures, metallic objects in the chest or brain, cardiac pacemakers, and somatic diseases associated with brain dysfunction were excluded from the study. Pregnancy, use of coercive measures, severe suicidal risk, severe agitation or delirium, and alcohol or drug dependence (ICD-10) constituted additional exclusion criteria.

General physical and neurological examination will be supplied by routine blod tests and an electrocardiogram.

Outcome measures

Primary effect measures: percentage of response and remission.

Secondary outcome measures: change in cognitive function.

Depression severity is evaluated using the Hamilton 17-item, the 6-item scale for depression (HAM-D6) and the Major Depression Inventory scale (MDI)

Response defined as a 50 % reduction in total HAM-D score and remission as a total HAM-D (17-item) score of 8 or lower.

Adverse effect is further assessed by a scale based on the Udvalg for Kliniske Undersoegelser (UKU: Committee for Clinical Investigations) side effect rating scale

Changes in the degree of depression and adverse effects will be assessed at baseline (before treatment) at weekly intervals within 24 hours after 3. 6. and 9. ECT. Additional HAM-D, MDI´s and UKU ratings are carried out 4 weeks after termination of the treatment period. Trained clinicians carry out quantitative and diagnostic ratings.

The cognitive function. Patients will be assessed before each treatment course, within 48 hours and 4 weeks after last ECT. Global cognitive functioning is assessed with a short test battery comprising measures of attention and speed (Trail-Making Tests A and B, visual and verbal memory and learning (Rey Complex Figure Test, Logical Memory/ Wechsler Memory Scale Revised, and Executive Function as in Verbal Fluency semantically and phonologically.

Pharmacological Treatment

Concomitant antidepressant treatment is monitored continuously during the investigation. During the treatment period (from baseline until the end of week 3), psychopharmacological treatment is held constant. If possible, benzodiazepines will be tapered off 2 to 3 days before the first ECT. In case of severe anxiety, oxazepam will be used before 5 PM the day before treatment. If sleeping medication was needed, zolpidem or quetiapine will be preferred. Antiepileptic's prescribed as mood stabilizers are discontinued (lamotrigine dose was halved) before the first treatment. After termination of the treatment period, the patients continue any psychopharmacological medication with no restrictions.

rTMS treatment was carried out by a MagPro type R30 (MagVenture A/S, Lucernemarken 15, 3520 Farum, DK) stimulator, which is certified by the EU for treatment of depression, using a water-cooled double blind, figure eight placebo spool (type Cool-B65 A/P Butterfly Coil.

The motor threshold will be determined by placing the center of the coil on a line connecting the vertex with the auditory meatus, stimulating the cortex to find the lowest intensity that produced a visual motor response in the tenar of the left hand. The treatment site over the right dorsolateral prefrontal cortex is then found by moving the coil 5 cm anterior to this point at a right angle to the line connecting the auditory meatus and the vertex.

The patients receive either placebo stimulation or two 180-second 1-Hz trains delivered at an intensity of 110% of motor threshold with a 180 seconds intertrain interval. This procedure is followed two times a week on ECT-free

days ie. on Tuesdays and Thursdays as ECT is delivered on Mondays, Wednesdays, and Fridays.

Blinding

The result of the randomization (active or sham rTMS) will be downloaded by an independent third part to a patient Key (USB memory stick) that will be sent to the treatment center and inserted in the MagPro stimulator.
The coil, which is identical on both sides, had a built-in position sensor used to ensure that the correct (active or sham) side of the coil faced towards the patient's head. If the coil position is wrong, the operator receive the display message a "Flip Coil" prompt on the MagPro screen. To ensure blinding of patients, electrodes from the MagPro will be used to stimulate the patient's skin in the coil area to mimic real rTMS.

Electroconvulsive Therapy

Thymatron (Fred Berninger Import OHG, Taufkirchen, Germany) (maximum dose of stimulation, 1008 milli coulombs) is used for ECT. Patients elected for this type of treatment received 9 ECTs on the average during the project period. The treatment is administered 3 times weekly with handheld electrodes according to the guidelines of the Danish Psychiatric Society .

Statistics

Treatment and placebo groups will be compared based on a t-test or chi-square test dependent on which was most suitable. The effect of treatment on $HAMD_6$,$HAM\text{-}D_{17}$ and MDI over time will be evaluated based on a last observation carried forward as well as quadratic linear mixed model. The effect of treatment on cognitive function over time will be evaluated based on a linear mixed model.