Rivastigmine for ECT-induced Cognitive Adverse effects in Late Life Depression: a multicenter, randomized, double-blind, placebo-controlled, crossover trial

No registrations found.

Ethical review	Not applicable
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON23967

Source
NTR

Brief title
Recall-study

Health condition

Depressive disorder, cognitive side-effects

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: ZonMW- Goed Gebruik Geneesmiddelen.

Intervention

Outcome measures

Primary outcome

Impact of rivastigmine on:

1. Scores on Delirium Rating Scale (DRS-98)(Van der Mast et al., 2004), assessed after two ECT sessions with rivastigmine, compared with DRS-98 outcomes assessed after two ECT sessions without rivastigmine.

2. Scores on cognitive functioning tests (MMSE, fluency, clock-drawing-test), assessed after two ECT sessions with rivastigmine, compared with outcomes assessed after two ECT sessions without rivastigmine.

Secondary outcome

- Impact of rivastigmine on several ECT characteristics measured (blood pressure, heart rate, seizure length, post ictal suppression index, seizure threshold, type of anesthetics and dosage) during ECT.

- Adverse/ side effects of rivastigmine.

- Profiles of confusional states based on scores on reorientation time, Richmond Agitation Sedation Scale (RASS), Confusion Assessment Methods (CAM)/Delirium Rating Scale (DRS-98), MMSE, fluency, clock-drawing-test, all assessed during ECT, and their determinants.

Study description

Background summary

Background:

Electroconvulsive therapy (ECT) is the most effective treatment for severe depressions. Unfortunately, several cognitive side effects with a large pallet of different manifestations and impact often occur. For instance, postictal agitation ((PIA) with ia motor restlessness and panic like behavior directly after ECT lasting 5 minutes till one hour), or more mildly general disorientation recovering within 1-2 hours after ECT, anterograde memory deficits and retrograde amnesia (both mostly reversible after a few weeks till several months) are well known. Finally, interictal delirium characterized by severe confusion which can appear separately form the postictal disorientation, taking several days to weeks to resolve, mostly in elderly individuals, has also been described (Selvaraj, 2012). In particular the latter may result in a premature abandoning of ECT, and hence failure to achieve remission of the depressive disorder.

Considering its beneficial effect on cognition in persons with mild to moderate Alzheimer’s dementia and the potential beneficial effect on memory deficits in ECT-treated persons with schizophrenia (Stryjer et al., 2012) and either major depressive disorder, bipolar or

schizoaffective disorder (Matthews et al., 2013), treatment with an acetylcholinesterase inhibitor (ie rivastigmine) might be useful for the prevention or reversion of the interictal delirium as well. Therefore we designed a randomised double blind placebo controlled crossover trial embedded in a large cohort-study on ECT-patients, to investigate whether rivastigmine treatment has a positive effect on the severity and duration of the interictal delirium. We hypothesize, that rivastigmine addition during ECT can diminish the interictal delirium, induced by ECT.

Main objectives:

The main aim of this study is twofold. We aim to (1) investigate whether rivastigmine can be used as a novel treatment to reduce ECT-induced interictal delirium and (2) to gain further insight into differences in determinants between inter-ictal delirium and adjacent cognitive disturbances induced by ECT, including post-ictal agitation and mild general disorientation of short duration.

Methods:

All admitted depressed patients formally diagnosed with the Composite International Diagnostic Interview (CIDI) and indicated for ECT, will be screened for inclusion in a cohort of ECT patients (n=250). Next, regular ECT-treatment starts, with twice weekly ECT. Patients, who develop interictal delirium assessed by a decline of the Mini Mental State Examination (MMSE) of at least 4 points, or meeting the criteria of a delirium assessed by the Confusion Assessment Method (CAM) (Inouye et al., 1990), both measured once weekly, are eligible for inclusion in the multicenter, randomized, double-blind, placebo-controlled, crossover trial on rivastigmine (n=38).

Intervention:

When a patient fulfils the inclusion criteria for the trial, a transdermal rivastigmine patch (group A) or placebo patch (group B) will be applicated the evening before ECT treatment and will be removed 24hrs after application. After two ECT sessions, group A will receive placebo treatment for two sessions and group B will receive a rivastigmine patch for two sessions.

Study objective

Electroconvulsive therapy (ECT) is the most effective treatment for severe depressions. Unfortunately, several cognitive side effects with a large pallet of different manifestations and impact often occur. For instance, postictal agitation ((PIA) with ia motor restlessness and panic like behavior directly after ECT lasting 5 minutes till one hour), or more mildly general disorientation recovering within 1-2 hours after ECT, anterograde memory deficits and

retrograde amnesia (both mostly reversible after a few weeks till several months) are well known. Finally, interictal delirium characterized by severe confusion which can appear separately form the postictal disorientation, taking several days to weeks to resolve, mostly in elderly individuals, has also been described (Selvaraj, 2012). In particular the latter may result in a premature abandoning of ECT, and hence failure to achieve remission of the depressive disorder.

Considering its beneficial effect on cognition in persons with mild to moderate Alzheimer's dementia and the potential beneficial effect on memory deficits in ECT-treated persons with schizophrenia (Stryjer et al., 2012) and either major depressive disorder, bipolar or schizoaffective disorder (Matthews et al., 2013), treatment with an acetylcholinesterase inhibitor (ie rivastigmine) might be useful for the prevention or reversion of the interictal delirium as well. Therefore we designed a randomised double blind placebo controlled crossover trial embedded in a large cohort-study on ECT-patients, to investigate whether rivastigmine treatment has a positive effect on the severity and duration of the interictal delirium. We hypothesize, that rivastigmine addition during ECT can diminish the interictal delirium, induced by ECT.

Study design

Major measurements: Baseline, T1 (=at inclusion in trila), T2=1 week trial, T3= after 2 week trial, T4: after ECT-course.

In addition: every week minor measurements of deperssion severity and cognition.

Intervention

Note: target sample size=250 for cohort, in order to include n=38 for trial.

Intervention:

After inclusion (e.g. the occurrence of interictal delirium), the randomized, placebo-controlled cross-over trial starts. The randomization will be organized with a simple Williams design. Patients will be randomly assigned to either the order Rivastigmine (Riv)-Placebo (Pla) or the order Pla-Riv in the treatment periods. Each period lasts for 2 consecutive ECT-treatments. Nineteen patients will be treated with the Riv-Pla order (4.6 mg patch, the night prior to ECT), hence: during two consecutive ECTs rivastigmine is administered, followed by two consecutive ECTs with placebo (Group A), and nineteen patients, with the opposite order (Pla-Riv). (Group B) After 4 treatments (=2 weeks), the blinding is ended and the patients will be treated with – for him/her- the most effective procedure. Tmax of rivastigmine patch is 10-16 hours. Hence, application the night prior to ECT results in optimal dosage during ECT. The patch will be removed after 24 hours.

Contacts

Public
GGZ inGeest, De Nieuwe valerius;

D. Rhebergen
Amstelveenseweg 589

Amsterdam 1081JC
The Netherlands
+31-6-22961166
Scientific
GGZ inGeest, De Nieuwe valerius;

D. Rhebergen
Amstelveenseweg 589

Amsterdam 1081JC
The Netherlands
+31-6-22961166

Eligibility criteria

Inclusion criteria

Patients, aged 55 years or older, fulfilling the Composite International Diagnostic Interview (CIDI) criteria of a Major Depressive Episode (not necessarily in the context of a Major Depressive Disorder only) and indicated for ECT-treatment will be asked to participate in the study. Written informed consent will be obtained from each patient, or- in case of inability to consent - will be obtained by his legal representative.

Inclusion in rivastigmine-trial:

Next, the occurrence of an interictal delirium is assessed by the Confusion Assessment method (CAM)) and Mini Mental State Examination (MMSE)). The CAM and MMSE are recorded as a routine follow-up in all ECT-cases by a trained research assistant or trained nurse, in general at Wednesday (if ECT is performed twice weekly at Tuesday and Friday). Participants with a CAM-score, indicating delirium, will be included in the trial. For a diagnosis of delirium by CAM, the patient must display: 1) Presence of acute onset and fluctuating discourse, and 2) Inattention, and either 3) Disorganized thinking or 4) Altered level of consciousness (Inouye et al., 1990). The MMSE is a screening instrument for measuring the severity of

cognitive impairment with good interrater and test-retest reliability (Folstein et al., 1975; Cockrell et al., 1988). Officially, the MMSE is not validated as a diagnostic tool for assessing delirium, but in our opinion it is a useful tool in our study population to diagnose interictal delirium. We claim, based on our clinical experience that interictal delirium not always behaves as a 'regular' delirium and therefore does not always meet the criteria for delirium as measured with the CAM. Hence, by screening for interictal delirium only using the CAM, eligible patients for the trial might be missed. Persons with delirium according to the CAM score or persons with a change in total MMSE-scores of -4 during ECT are eligible for inclusion in the rivastigmine trial.

Exclusion criteria

Exclusion criteria are comorbid medical conditions that are a contraindication for ECT according to the prevailing Dutch ECT-guidelines (Van den Broek et al., 2010). Also, in case of prior participation in the study (in case of relapse of the depression requiring a new ECT course), the patient will be excluded.

Rivastigmine trial:

Exclusion criteria for rivastigmine-trial are prior participation in the study (in case of relapse of the depression requiring a new ECT course), bradycardia or AV conduction disorder (first degree AV-block excluded), already use of rivastigmine, galantamine or donepezil (all cholinesterase inhibitors for mild to moderate Alzheimers disease) or any previous allergic or adverse reactions to rivastigmine. Also individuals who switch from right unilateral electrodeplacement (RUL) to bilateral electrodeplacement (BL) during trial will be excluded.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-09-2017
Enrollment:	250
Type:	Anticipated

Ethics review

Not applicable

Application type:	Not applicable

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL7116
NTR-old	NTR7321
Other	2014-003385-24 : EudraCT

Study results