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

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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...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Deliria (incl confusion)
Study type	Interventional

Summary

ID

NL-OMON47261

Source
ToetsingOnline

Brief title
Rivastigmine for ECT-induced Cognitive Adverse effects

Condition

- Deliria (incl confusion)

Synonym
delirium, Interictal delirium

Research involving
Human

Sponsors and support

Primary sponsor: VUmc
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Cognitive advserse effects, delirium, Electroconvulsive therapy, Rivastigmine

Outcome measures

Primary outcome

1. Scores on Delirium Rating Scale (DRS-98), 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.

NB baseline scores: mainained 48-24h before first ECT session within trial.

Secondary outcome

3.Impact of rivastigmine on several ECT characteristics (bloodpressure, heart rate, seizure length, post ictal supression index, seizure threshold, time of - anesthesia induced - muscle relaxation, type of anesthetics and dosage) measured during ECT.

4.Adverse/ side effects of rivastigmine.

For differentiation into subtypes of confusional states and their determinants:

5. 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, Stroop Color Word Test, Rey Auditory Verbal Learning Test (=15-word learning test), fluency, clock drawing test, Kopelman Autobiographical Memory Interview, Visual Association Test (VAT) all assessed during ECT, and their determinants.

7. What is the Cost effectiveness of rivastigmine addition during ECT? For this purpose we assess the EQ-5D-5L at baseline, at the start of the trial and after ECT.

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 and 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 and may take 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, 2012) and either major depressive disorder, bipolar or schizoaffective disorder (Matthews 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 objective

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. The main research questions are as follows:
1. Can rivastigmine 4.6 mg AN diminish the severity of ECT induced interictal delirium?
2. What are the predictors of interictal delirium among depressed persons during ECT?
3. What are the predictors of rivastigmine treatment response?
4. Does rivastigmine affect ECT parameters such as bloodpressure, heart rate and seizure threshold and time of - anesthesia induced - muscle relaxation?
5. What is the tolerability of rivastigmine during ECT? Which side-effects occur?
6. Do determinants of inter-ictal delirium and adjacent cognitive disturbances induced by ECT, including post-ictal agitation and mild general disorientation of short duration, differ?
7. What is the Cost Effectiveness of rivastigmine during ECT?

Study design

It is a double blind randomised placebo controlled crossover study, embedded in a large cohort study on ECT patients.

Eligible patients or their proxies will be verbally informed by their doctor on the content of the study, benefits and risks, and will receive a patient information folder on the nature of the study (version number, see appendix). The time to consider participation to the trial will be 24 hours maximum. Subsequently the patient or their proxy is asked for informed consent for separately:
- participation to the large cohort
- participation to the trial

After obtaining written informed consent, the patient will be included in the large cohort and will receive treament according to standard care. Extra researchdata will be obtained (see burden and risk section)
ECT will take place twice a week.
One day after ECT the patient will be

One day after ECT the patient will be assessed on the presence of the interictal delirium by

1. Meeting the criteria of a delirium by the Confusion Assessment Method (CAM). 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 consciousnes
2. Decline of the Mini Mental State Examination (MMSE) of at least 4 points

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.

Intervention

Both study arms will receive standard hospital care troughout the trial.

Each patient who signed informed consent and meets the criteria for interictal delirium will be randomized to one of both treatment arms (A or B).
In arm A a rivastgmine patch will be applicated during two consecutive ECT sessions for 24 hrs (application the evening before ECT and removal after 24 hrs). The next two consecutive ECT sessions, the patient will receive a placebo patch.
In B, the patient will receive the patches in opposite order: the first two sessions a placebo patch for 24 hrs and the two consecutive sessions a rivastgmine patch.

Study burden and risks

The dosis if the rivastigminepatch is the minimum dose and individuals are only exposed 2 times during 24 hrs to the drug. Side effects will be closely monitored
There will one extra venipuncture and collection of two urine morning samples for the cohort. Many examinations are part of standard care. Additions to common clinical practice are: Apathy-scale, IPAQ, 2 times Short Physical Performance Battery (SPPB, including 3 timed performance tests: walking speed, Tandem stand for balance and chair stand test) 2 times handgrip strength and EEG, all non-invasive methods.
After each ECT session several cognitive tests and a side effects questionnary (see section primary and secondary outcomes) and till 90 minutes after ECT maximum reorientation time will be assessed both in the cohort as during the trial. Side essects questionnary will be held for six times.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

First part (cohort)
- Age: 55 years or older
- Patient is admited at the in-wards of one of the participating psychiatric hospitals
- Patients fulfilling the Composite International Diagnostic Interview (CIDI) criteria of a Major Depressive Episode not necessarily in the context of a Major Depressive Disorder only)
- Patient is indicated for ECT-treatment.
- Patient or legal representitive is able to give informed consent;Adjuvant criteria for inclusion in the rivastigmine trial
- Occurence of an interictal delirium is assessed by the Confusion Assessment method (CAM) and/ or 4 pts drop Mini Mental State Examination score (MMSE)

Exclusion criteria

First part (cohort)
- Patient does not meet the inclusion criteria
- Patient has a comorbid medical condition that is a contraindication for ECT according to the prevailing Dutch ECT-guidelines
- Prior participation in the study (e.g. in case of relapse of the depression requiring a new ECT course).;Adjuvant criteria for exclusion in the rivastigmine trial
- Current use of rivastigmine or an other cholinesterase inhibitor
- Known intolerance of rivastigmine or an other cholinesterase inhibitor
- Bradycardia or AV conduction disorder at baseline ECG (first degree AV block exluded)
- switch from right unilateral electrodeplacement (RUL) to bilateral electrodeplacement (BL) during trial

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-08-2017
Enrollment:	170
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Exelon
Generic name:	Rivastgimine

Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	09-03-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-09-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-05-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
EudraCT	EUCTR2014-003385-24-NL

Register	ID
CCMO	NL50824.029.15