Clinical Research Centre for Neuromodulation in Psychiatry

Research Project - 1 Information booklet
Title:

Comparative clinical efficacy and neurobiological correlates of true-vs-sham ECT in patients with clozapine-resistant/intolerant schizophrenia

Introduction

This research study is being carried out at the Departments of Psychiatry at (1) NIMHANS, Bengaluru; (2) Central Institute of Psychiatry (CIP), Ranchi and (3) Kasturba Medical College, Manipal with due approval by the respective Institute Ethics Committees. This multi-center research project is funded by the Wellcome Trust – Department of Biotechnology India Alliance.

Why am I being approached for participation in this research?

We are conducting research to examine the effect of a method of treatment called electroconvulsive therapy (ECT) in individuals with schizophrenia who have not experienced improvement with a medicine called clozapine or are unable to tolerate this medicine. We understand that your doctors have advised you ECT as you are suffering from schizophrenia and your symptoms have not improved to a satisfactory extent despite receiving medicines including clozapine or your doctors cannot give you an optimal dose of clozapine due to adverse effects. We are requesting you to participate in this study in this background. Your doctor has already briefed you about ECT. You may learn more about ECT in the information booklet that has been provided to you; we are also going to explain to you about it in more detail. In short, in this treatment, we provide anesthesia to a patient and then induce seizures for a few seconds using a small dose of electric current. We believe that you are suitable to participate in this study.

What is the purpose of the study?

ECT was invented nearly 8 decades ago as a treatment for schizophrenia. Doctors have been using it for treating schizophrenia. However, its benefits in schizophrenia, particularly for those who have not experienced improvement with medicines, has not been established beyond doubt. As we said earlier, during ECT, anesthesia is administered. Earlier research has shown that some patients who receive anesthesia alone, without electrically induced seizures, also experience improvement. This is also known as sham ECT. To know whether ECT is indeed helpful, the outcomes of patients who receive true ECT (i.e., anesthesia and ECT) should be directly compared with outcomes of those who receive sham ECT. The most important purpose of this study is to compare the effects and adverse effects of true ECT with sham ECT.

Doctors have observed that some patients experience improvement with ECT, and others do not. Currently, we are unable to predict which patients experience improvement. The second purpose of this study is to identify predictors of response to ECT, using research investigations (details provided below). In addition, this research might help us to understand the mechanism by which improvement occurs.

What tests will be performed in this research?

In the following sections, we provide information regarding the various research investigations/tests that are employed in this research which we hope would address most of the

questions that you may want clarity on before deciding to participate in this study. In addition to the information provided in these sections, you will be shown a video of all these procedures (electroconvulsive therapy (ECT) as well as all other research techniques) so that you can understand them better.

Research Investigations

The research investigations that will be done in this study include: Magnetic Resonance Imaging (MRI), electroencephalography (EEG), electrocardiography (ECG), neuromodulation tests, detailed clinical assessments and blood sample collection. These investigations will take about 5 hours altogether. They will be done with adequate breaks & refreshments over a period of 1 or 2 days to ensure your comfort.

Magnetic Resonance Imaging (MRI)

MRI scan tests will help us to understand the structure, activation, connections, and chemical nature of the brain. We will be doing some related scanning procedures to make sure that you do not have any neurological disease as well as to meet the needs of specialized research studies. The duration of the MRI scan will be for about 1 hour.

The MRI scan uses a large magnet to obtain the scans and does not use radiation like X-rays. During the recording, you will be asked to lie on your back on a table with your head positioned in a padded headrest. The study coordinators and the MRI technicians will provide you with the necessary instructions and help during the recording.

If we notice any obvious brain structural abnormalities in your scan, we will inform you regarding the same and counsel you about the options for further treatment. If you so wish, we would refer you for consultation with the appropriate specialist for obtaining the necessary guidance regarding treatment. You will be provided with a printed report on structural MRI scan findings. Decisions would be taken in consultation with your treating team.

Though the MRI scan procedure is considered very safe, in extremely rare situations, there may be certain risks and discomforts associated with the same. Some people may get muscle aches and pains from lying on their back. This will be minimized by providing cushions at pressure points and beneath the knees as required. Earplugs or headphones will be used to dampen the sound inside the MRI room. You may feel nervous about being in a small space when you are in the MRI scanner; however, you will be able to communicate with us throughout the scan and can tell us whenever you want the scan to be stopped or interrupted.

The following items may interfere with MRI scans and some can be potentially hazardous: E.g., If you have any of these items in your body, participation in the study could cause serious harm. Therefore, it is very important for you to notify the researcher if you have any of these items in your body and to avoid participating in this study. Please be reassured that we will also be examining you thoroughly to make sure that you do not have these items in your body.

Electroencephalography (EEG)

An electroencephalography (EEG) (or brain wave test) measures the electrical activity in the brain (brain waves) using electrodes (small metal discs or sensors) placed on the head with gel. The test does not hurt and usually takes about an hour. During EEG recording, you would be made to

lie down comfortably. We would fix a net outside your head comprising of EEG recording electrodes which would be connected to the EEG amplifier. You will remain awake throughout the duration of the EEG recording. We will be doing some related EEG procedures to make sure that you do not have any neurological disease.

Electrocardiography (ECG)
An electrocardiography (ECG) is a test that gives us a measure of the heart's electrical activity. At the same time of EEG recording, your ECG will also be recorded. Like MRI, EEG as well as ECG also are absolutely safe procedures and do not involve any radioactive or other significant risks.

Neuromodulation Tests

Neuromodulation tests are performed to understand the reactivity of brain cells (neurons). We will do the neuromodulation tests using non-invasive and safe brain stimulation techniques namely – Transcranial Magnetic Stimulation (TMS) and transcranial Direct Current Stimulation (tDCS).

Transcranial Magnetic Stimulation (TMS): In this method, the brain is stimulated using a magnetic field through a coil attached to a machine. The person sits comfortably on a chair. The magnetic coil will be placed on the head (scalp) to stimulate the brain region that represents your right thumb and the activity levels of right thumb muscle will be recorded using leads placed on the right hand. The coil makes a ticking sound every time the brain is stimulated. The person remains awake and alert during the session

Transcranial Direct Current Stimulation (tDCS): tDCS procedure involves the application of weak, battery delivered direct current (2 mA) through electrodes on specific parts of the head. Please note that the batteries are part of the equipment and will not be placed on the subjects.

Details of Neuromodulation Tests Procedure:
The neuromodulation tests will take approximately 1 hour with adequate breaks in between to ensure your comfort. You will remain alert and awake during the whole session. The procedural details of these tests are as below:

- You will sit comfortably on a chair with hands rested on hand-rests. 3 electrodes will be attached to different areas of your right hand to record muscle activity. The TMS coil will be placed on the left side of your head and some brain reactivity recordings will be done. There will be twitches on your hand.
- After this, active or inactive tDCS will be used to stimulate your brain for 20 minutes. - After this, the same brain recordings which we have done using TMS coil earlier will be done again.

Please note that after the neuromodulation tests session, you will be able to leave immediately and do all the activities including driving.

Clinical Assessments
In addition to the above investigations, we shall carry out a detailed evaluation of your medical, neurological and psychiatric status by examining you as well as by interviewing you in detail. We may seek additional information from other close relatives (e.g., spouse or children or other caregivers)as well as from your previous medical records. The study will involve you doing some computerized and paper-pencil tests for assessment of brain functions such as attention,

concentration, memory, planning, and reasoning. All these assessments & tests will take about 2 hours.

Blood Sample Collection

A 15 ml sample of blood (about 3 teaspoons) will be collected for clinical blood investigations as well as research studies involving genetics and other assays. If any abnormality is found in clinical blood investigations, we will suggest the required treatment / refer you to another specialist doctor as appropriate. The blood sample (serum, plasma, and DNA) will be stored and utilized for genetic tests of this project as well as for future research assays, that will be conducted after due approvals from the Institutional Ethics Committee.

What are the risks associated with these research investigations?

All the investigations/tests planned in this study are found to be mostly safe and are not commonly associated with any significant risks or adverse effects. This safety of these investigations is established through previous observations from numerous research studies conducted by us as well as other researchers internationally.

MRI: This does not involve any risk apart from tolerable discomfort during procedures.

EEG: The gel used to put the discs on your head is sometimes sticky and the discs may scratch a little bit.

ECG: The test may occasionally cause some redness or itching where the pads are placed. These effects (redness/itching), if it happens, will disappear after some time.

TMS: During stimulation with TMS, you may experience mild pain over your scalp. Most people tolerate this well. However, if you find it intolerable, let us know. We will take appropriate measures. Extremely rarely, TMS has caused individuals to experience seizures. International professional bodies have provided guidelines to minimize the risk of seizure and we would strictly adhere to these. Please be reassured that our lab has required medicines and expertise to treat seizures immediately if it occurs in spite of these precautions.

tDCS: Sometimes, during the tDCS, you may experience mild and tolerable tingling/itching in the place where the tDCS electrodes are positioned near / on your scalp. However, these sensations are tolerable and most often transient – i.e. will disappear within 2 or 3 minutes. At the maximum, these tolerable sensations will be present usually only during the period of administration of tDCS. Very rarely, you may get mild headache or discomfort. In such situations, the required medical help will be provided.

Blood Sample Collection: The collection of the blood sample is expected to be minimally painful. All aseptic precautions will be taken during the procedure.

What will happen in this research study if I take part?

There are two parts to this study (please refer to the flow chart provided at the end of this consent form).

Part-1: In the first part, you will be assessed with questionnaires and research investigations (cognitive function tests, MRI brain scan, electroencephalography (EEG) & electrocardiography (ECG), TMS based tests as well as blood sample collection). After that, you will be given one of the two treatments: true ECT or sham ECT as pre-determined by computer-generated choice. You

have an equal chance of receiving either of these. We would administer these on alternate days for 9 sessions. In either treatment, you would receive anesthesia as determined by our anaesthesiologists. If you happen to be in the true-ECT group, then you would additionally receive an electrical stimulus as described in the ECT information booklet. The rest of the care during the treatment sessions would remain identical in both treatments.

During anesthesia, the anaesthesiologist will provide general anaesthesia by administering medicines through your veins to keep you unconscious, in addition to medicines that relax your muscles. During the procedure, your vital signs like heart rate, heart rhythm, blood pressure, and oxygen level will be monitored. Additional monitoring may be performed based on your medical condition. The anaesthesiologist will perform a pre-anaesthesia check prior to the procedure. Anesthesia will be administered only if you are found to be fit enough to receive anaesthesia. If you are suffering from any other co-existing illness or your blood investigations are found to be abnormal, you will be referred to a suitable physician for evaluation and optimisation of your condition to facilitate safe anaesthesia. Anaesthetic drugs can interact with your existing medications and may occasionally lead to side effects.

The risks and potential complications during anaesthesia for ECT include, but are not limited to: frequent/minor - nausea, vomiting, confusion, headache, body ache, muscle stiffness, memory problems, airway secretions, changes in heart rate and blood pressure. Rare/major problems include – awareness of procedure, inability to breathe or difficulty in breathing, lip/tongue/teeth injury, delayed recovery, aspiration pneumonia, anaphylaxis (potentially fatal allergic reaction), organ failure (heart, lung, liver, and kidney) and very rarely, death can occur due to unanticipated complications during anaesthetic procedure. Complications may also arise as a result of the patient's condition. All or any of these factors may lead to a decline in medical status. In the event of any complication, physicians and staff of NIMHANS will administer all necessary treatment, including cardiopulmonary resuscitation if needed. The severity of complications may warrant transfer to ward/casualty/ICU to continue the necessary care.

We will monitor your symptoms and adverse effects after each session of treatment. We may reduce the frequency of sessions if we observe a significant problem with your concentration, memory and other mental abilities. After the 9th session, we will terminate the ECT course if there is no improvement from the previous session on three consecutive sessions. Irrespective of the number of sessions, we would terminate ECTs in any of the following situations: (1) complete improvement of your condition (2) there is severe impairment in your concentration, memory and other mental abilities; (3) medical conditions because of which ECTs should be withheld; (4) whenever you wish for whatever reason. We will be reassessing you with questionnaires & all tests except blood sample collection after terminating the treatment. If you improve significantly after this, your participation in this research will be completed. If you receive sham ECT and if you do not experience adequate improvement, then you will have the option to participate in the second part of the study. Please note that during the first part of the study, you will not know whether you are receiving either true or sham ECT. We do this in order to reduce the effect of your expectations on the effects and adverse effects of the two treatments.

Part-2: During the second part of the study, we will treat you with 9 sessions of true ECT. The decision on the frequency of sessions and when to terminate the treatment would be the same as described above. As happened during the first part of the study, all the above-mentioned research investigations (except blood sample collection) will be repeated before and after ECT.

As we have mentioned earlier, you will have the freedom to withdraw your consent at any time during the study. Moreover, we will be requesting your consent again before starting the second part of the study.

What are the potential benefits and risks of participating in the research?

If you do not take part in this study, your doctors may suggest different treatments to you, which may include ECT. If you take part in this study and if you end up receiving true ECT, your treatment would be the same as you would have received otherwise. However, if you end up receiving sham ECT, then there is a possibility that your improvement would be slower than with true ECT. However, since electricity is not used to induce seizures, you may experience less adverse effects than with true ECT, i.e., you may experience less disturbance of your concentration, memory and other mental abilities and fewer chances of experiencing headaches. Please keep in mind that you may not experience improvement with either of these treatments. Also, please keep in mind that the risks of anaesthesia (which are described in the ECT leaflet) are the same in both treatments.

What will happen if I benefit from one of the treatments?

After the completion of these treatments, this research study will be completed. However, in consultation with your treating doctors, we will discuss with you and would decide about the future course of your treatment. It may or may not include ECT.

What will happen if both treatments do not help me?

After the completion of these treatments, this research study will be completed. However, in consultation with your treating doctors, we would decide about the future course of your treatment. Since you would not have improved with ECT, your future treatment may not include ECT.

What if I feel uncomfortable during the treatment procedure?

In case you develop discomfort to the level that you wish us to discontinue it, we would oblige and stop the procedure.

How long will these procedures take?

All the investigative procedures (MRI, EEG, ECG, neuromodulation tests, clinical assessments, and blood sample collection)will altogether take about 5 hours. The time taken for ECT procedures is provided in the leaflet.

How many times these tests will be performed?

During part-1 of the study these tests will be done twice (i.e. before and after the neuromodulatory treatment). During the part-2 of the study, the test will be done once after the completion of the neuromodulatory treatment.

Is it compulsory for me to take part in this research?

Participation in this research is optional and it is voluntary, meaning that the decision to take part in this study will be as per your wish. You will be given a copy of this information sheet and have an adequate time to read through, think and ask any questions before deciding. If you do decide to take part you will be asked to sign a consent form and given a signed copy of the consent form to keep. If you decide to take part you are still free to withdraw at any time during the study without giving a reason. A decision to withdraw or not to take part, will not affect in any way your routine medical care here.

Would my denial to participate in the study hinder me from receiving regular treatment?
Your refusal to take part in this study would be duly respected by us and, irrespective of your participation in this study, you would continue to receive the best possible treatment from your doctor without any prejudice. Please note that even if you are not participating in this research study, you may still receive ECT under anesthesia as described above as a treatment for your symptoms as recommended by your treating doctor.

Will there be any modifications made in the current treatment that I have been prescribed for my symptoms?
The treatments will be administered independently of other treatments and will not influence the treatments that you are prescribed by your treating team.

Will my treating doctors be informed about my condition?
We will consult your doctors whenever we take any important decisions. E.g., if you develop any complications / significant worsening of your condition/termination from the study, etc

Will I be obligated to complete my participation in this study once I agree to sign the informed consent?
No. There is no obligation of any kind. Even if you have agreed and signed the informed consent, you are free to withdraw whenever you wish too, with no justification required.

Do I have the choice to withdraw my choice of participation at any time of the study? If I withdraw, do I have to justify or give reasons for the same?
Yes, you can withdraw anytime you wish to. You can willingly share with us your concerns and reasons for backing out of the study. But you are not obligated to tell us your reasons. If you do not wish to confide in us, no questions will be asked.

Can I ask, enquire or question any doubts I have during the entire time of my participation in the study?
Anytime during the study, you are free to clarify your doubts and questions with respect to the research procedure.

Do I have to pay anything from my side for the tests or procedures that are a part of the study?
As you are participating in the study, all your tests and procedures are carried out for the research purpose. You do not have to pay anything from your side.

Will there be any reimbursement for my travel expenses?
Yes, we will compensate for your time and incidental expenses including travel and refreshment costs.

How likely is that I might suffer from any injury attributable to my participation in the research procedures? If any such injury happens, will I be compensated?

We will implement all the research procedures taking utmost care to avoid any injury. In the unlikely event that you suffer any injury attributable to your participation in the research procedures of this project, you will be compensated financially as per the National Ethical Guidelines for

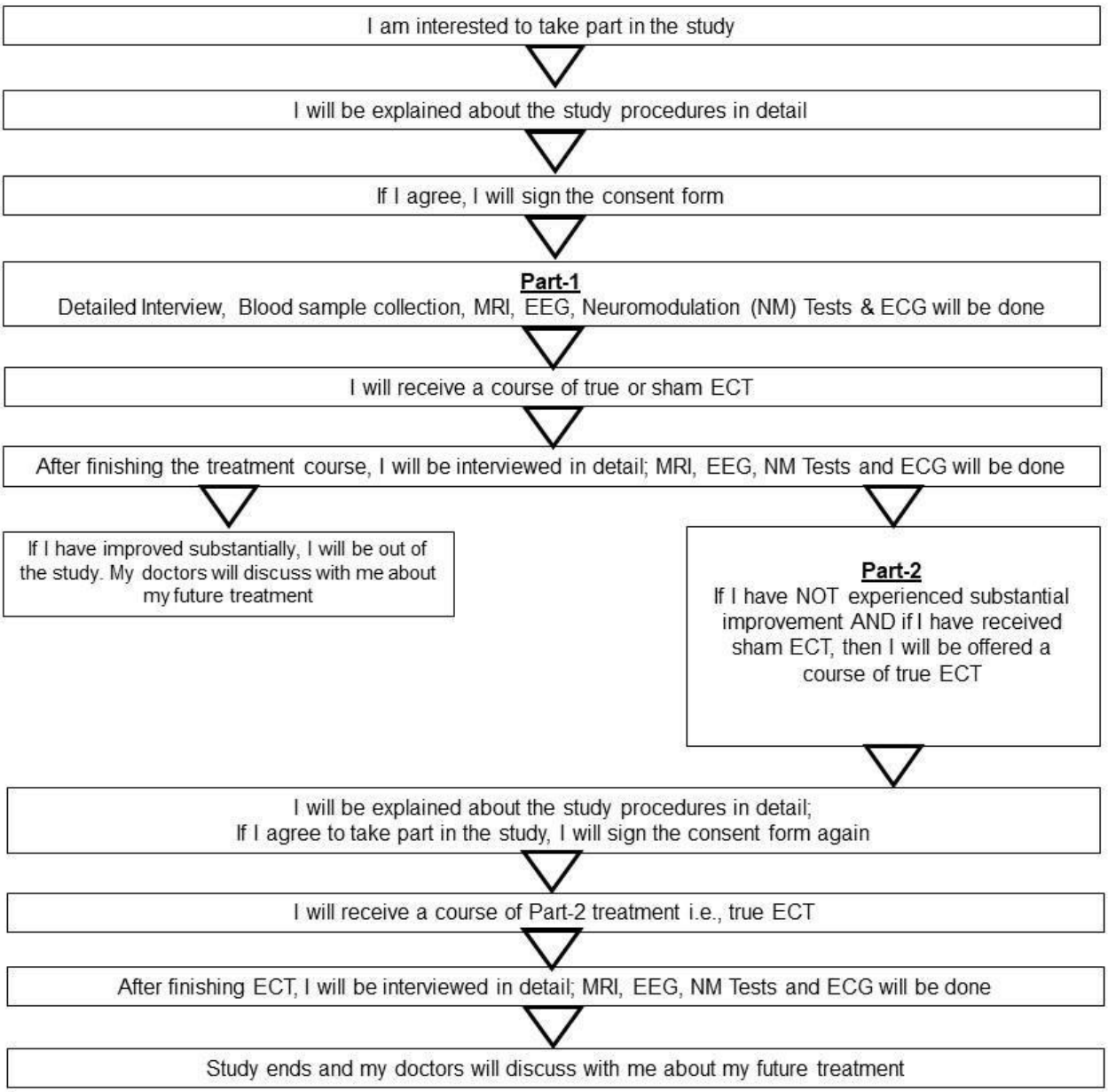
Biomedical and Health Research involving Human Participants by the Indian Council of Medical Research.

Will the test results obtained in the study be made available to others? Will my participation confidentiality be maintained?

Your identity will be completely protected. All information from the study will be stored under code to maintain strict confidentiality and will be reviewed only by the investigators, ethics committee or regulatory bodies. This coded and de-identified data (and its copies) will be stored in an encrypted format with password protected and secured access control in the database of computer servers at NIMHANS, collaborating institutes, cloud storage and any other storage media. This data will be used for further advanced analyses as well as future research studies. If you agree, as per the guidelines of scientific organizations and with the approval of relevant regulatory bodies, your data (in coded and de-identified format) will be shared with interested national and international researchers/collaborators, working on similar/related research ideas to foster greater understanding of the results; this, in turn, may lead to the larger good of patients suffering from depression and other diseases as well as scientific advances worldwide.

Flow Chart: Sequence of Research Procedures

Project-1: Comparative clinical efficacy and neurobiological correlates of true-vs-sham ECT in patients with clozapine-resistant/intolerant schizophrenia



Note:
You may withdraw from the study any time.
We will discuss with you and your doctors about future course of your treatment if you wish so.