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Review Article

Electroconvulsive Therapy (ECT): Important parameters which influence its effectiveness

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Abstract

Electroconvulsive therapy (ECT) is usually given to people with severe depression which has not responded to other forms of treatment such as anti-depressants. However, it is sometimes used for people with a diagnosis of bi-polar disorder or schizophrenia. It was originally developed in the 1930s and was used widely during the 1950s and 1960s for a variety of conditions. ECT consists of passing an electrical current through the brain to produce an epileptic fit – hence the name, electro-convulsive. The idea developed from the observation that, in the days before there was any kind of effective medication, some people with depression or schizophrenia, and who also had epilepsy, seemed to feel better after having a fit.

The mechanism of action of ECT is not fully known. ECT affects multiple central nervous system components, including hormones, neuropeptides, neurotropic factors, and neurotransmitters. The induction of a bilateral generalized seizure is required for both the beneficial and adverse effects of ECT. Certain parameters like seizure duration, electric stimuli, seizure threshold, ECT practice factors and medication can influence its efficacy or effectiveness. This study aims to review the evidence base of these parameters in detail.

Keywords: A review of literature regarding ECT was using search engines like MEDLINE, PsycInfo, and OVID using the key words "electroconvulsive therapy," "seizure parameters," "seizure duration," "seizure threshold," "stimulus dosing" and "effectiveness."

Introduction

Electroconvulsive therapy (ECT) is an effective treatment for some individuals with severe neuropsychiatric illness. It is widely used to treat certain psychiatric disorders, particularly major depression.[1,2] ECT involves applying a brief electrical pulse to the scalp after the patients are administered muscle relaxants and general anaesthesia.[3] This pulse excites the brain cells causing them to fire in unison and produce a seizure.

In 2003, the National Institute of Clinical Excellence (NICE) issued guidance on the use of ECT. Its use was recommended only to achieve rapid and short-term improvement of severe symptoms after an adequate trial of treatment options has proven ineffective and/or when the condition is considered to be potentially life-threatening in individuals with severe depressive illness, catatonia or a prolonged manic episode.[4]

The mechanism of action of ECT is not fully known. ECT affects multiple central nervous system components, including hormones, neuropeptides, neurotropic factors, and neurotransmitters. The induction of a bilateral generalized seizure is required for both the beneficial and adverse effects of ECT. Certain parameters like seizure duration, electric stimuli, seizure threshold, ECT practice factors and medication can influence its effectiveness. The degree to which electrical stimulation exceeds the seizure threshold, the positioning of electrodes on the head, pulse width, pulse frequency and seizure duration are all known to be important.[5] This study aims to review the evidence base of these parameters in detail. The seizure duration and electric stimulus are the two critical parameters and are therefore the main focus of this review.

Literature Review

A review of literature regarding ECT was using search engines like MEDLINE, PsycInfo, and OVID using the key words "electroconvulsive therapy," "seizure parameters," "seizure duration," "seizure threshold," "stimulus dosing" and "effectiveness."

Parameters Associated with Effectiveness of ECT

- Seizure Duration
- Electrical Stimulus
- Seizure Threshold
- ECT Practice Factors
- Endocrine Factors
- Medication
- Other Parameters

Relationship between Seizure Duration and Effectiveness of ECT

Very little is documented on clinical studies that correlate ECT effectiveness and seizure duration. There is evidence that supports the direct relationship of seizure duration and the effectiveness of ECT. It was thought that measuring the seizure duration and the knowledge of measuring such parameters can help explain its therapeutic effect.[6] There has been research which suggests that motor seizures of less than 15 seconds in

duration do not exhibit tonic-clonic phases and are ineffective in treatment.[7] Some of the studies in past years found a direct relationship between total seizure duration during a course of treatment and patient response to ECT.[8]

A retrospective study on ward patients found that a positive clinical outcome from depressive symptoms has a direct relationship with accumulative seizure time in the course of therapy.[8] However, the study was neither randomized nor controlled. Stimulus intensity, diagnosis, and concurrent medication parameters were not properly considered. Another study that supports the correlation found that 88% of patients with cumulative seizure time of 300 seconds and over had a favourable response. The data was retrospectively and prospectively collected in a university hospital. It was mentioned that data gathering was very difficult specifically with regard to the variable number of patients' ECT sessions; the confounding effect of medication and the treatment of different patients using unilateral or bilateral.[9]

However other studies challenge these statements. A prospective study of a sample of depressed patients undergoing ECT, the seizure duration did not correlate with Hamilton Depression Rating Scale (HAM-D) scores after treatment. However, it was found that significant nonverbal memory loss of patients was correlated with seizure duration.[10] The seizure duration does not directly influence the frequency of ECT, longer seizures do not equate to fewer ECT treatments. Studies using HAM-D scores do not support the idea that seizure duration is a variable correlated to efficacy.[11] Short seizures during ECT for few patients are the result of a medical condition or drug treatment interference. On the other hand, patients who have been subjected to ECT treatment encounter shortened seizures.[12]

There are studies which show that the length of the cerebral seizure activity or the tonic–clonic convulsion is not related to clinical effectiveness.[6,13] However, the treating psychiatrist should question whether, or not, generalised cerebral seizure activity had occurred if, at the first treatment, the convulsion lasted less than 15 seconds or the EEG recording showed seizure activity lasting less than 25 seconds.[14] Such brief seizure activity might be the result of a focal or partial seizure, and therefore be of questionable therapeutic efficacy. It has been noted that there are patients who recover with ECT and yet display only short tonic–clonic convulsions. This may be more likely in elderly patients.

Most recent evidence mentions that the quality of cerebral seizure activity and the quality of the desired activity cannot simply be related to its length in time alone. It is recommended that the convulsion be timed from the end of electrical stimulation to the end of generalised, that is, bilateral, clonic activity. EEG monitoring can also be done but one needs to have good experience using this technique and sometimes artefacts can cause misinterpretation of the results.[15]

Relationship between Electric Stimulus and Effectiveness of ECT

ECT is administered by a constant-current, brief-pulse ECT machine that is able to deliver a wide range of electrical dose, that is, 25–50 mC up to 750–800 mC. It is recommended that new machines deliver a range of dose from 25 to 1000 mC.[15] One of the important parameters in predicting clinical response is the degree to which the electrical stimulus exceeds the seizure threshold.[16] The maintenance of adequate seizure duration on patients is a complicated issue. Elderly patients are also more susceptible to cognitive side effects than younger patients.[17] Patients regularly treated with ECT have records of shorten seizure duration over time, and clinicians need to increase stimulus to maintain duration, which in the long run can lead to complications.[18]

Electroencephalography (EEG) Findings

Voltage Suppression Studies. Postical voltage suppression refers to the decrease in resting EEG voltage after seizure activity as compared with baseline. Proper excitation of seizures invoke voltage-suppressing neural mechanisms intended to terminate and further seizure activity. This suppression is considered as a lower baseline on the EEG post ictus.[19]According to studies, the degree of suppression correlates with seizure generalization, therapeutic adequacy, and bilateral stimulation.[20]

EEG Waveform Features. Greater ictal EEG amplitude, intensity, and symmetry obtained with bilateral ECT are not common with longer seizures, but they are related to antidepressant outcome.[21] Studies found that the immediate post stimulus and mid ictal EEG amplitudes correlated with seizure therapeutic adequacy in depression. The symmetry of waveforms at the midpoint on the EEG tracing was also predictive.[20] It was also proven that seizure duration had no impact as an EEG measure of treatment adequacy.[21]

Seizure Charge. The calculated product of EEG voltage, seizure uniformity throughout the brain, and seizure duration was hypothesized to be a measure of treatment intensity and efficacy.[21] The variables included in total seizure charge are not physiologically independent of one another, which means longer seizure duration will not guarantee better results.

Low-dose bilateralelectroconvulsive therapy has a powerful antidepressant effectbut low-dose right unilateral therapy is ineffective.[22] Evidence shows that the efficacy of rightunilateral electroconvulsive therapy depends on the electricaldose.[23,24] There is some research showing that forboth unilateral and bilateral ECT, a higherelectrical dose leads to a more rapid clinical response.[7,17,23]

Seizure Threshold and Electroconvulsive Therapy

The knowledge of the seizure threshold is a guide to the selection of the electrical stimulus dose for ECT. In theory, the

seizure threshold is the lowest dose of electrical charge for each particular patient that is required to induce seizure.[25] In clinical applications the seizure threshold depends on individual patient's characteristics, treatment history, and other stimulus factors.[26]

The therapeutic effectiveness of ECT is partly dependent on the degree that the stimulus intensity exceeds the seizure threshold.[27,28] This statement is true on unilateral non-dominant electrode placement (UL) and on relative stimulus intensity. On bilateral (BL) ECT, the therapeutic response frequency is dependent on higher relative stimulus intensity,[28]whereas barely suprathreshold UL ECT has significantly reduced antidepressant potency in contrast to moderately suprathreshold UL ECT (150% above threshold).[6] The clinical use of this can be applied after determining the seizure threshold at the first treatment.[22,29] The desired relative stimulus intensity to be maintained during treatments is confounded by variable increase in seizure thresholds during treatment.[28] This rise in the seizure threshold lessens the degree to which a fixed stimulus dosage exceeds the seizure threshold which can result in possible diminished treatment therapeutic potency.

The seizure threshold can be higher in the elderly population and this may increase the difficulty of eliciting effective seizures.[29,30,31] The choice of anaesthetic agent and other age related factors can also affect the seizure threshold. Propofol can reduce the seizure duration and has a possible effect on the seizure threshold.[32] The seizure threshold may sometimes rise during the course of therapy. The dose would usually rise *pari passu* with a rise in the seizure threshold to maintain the dosing strategy. The seizure threshold can increase about 80% in bilateral ECT and 40% in unilateral ECT over a course of treatment.[6] Some studies found increases of only 25–40% for bilateral ECT.[33]

ECT Practice Factors and Seizure Duration

As discussed earlier, the success of ECT treatment can be related to the degree to which the electrical stimulus exceeds seizure threshold and not the absolute dose that determines clinical outcome, especially in unilateral patients.[6]Right unilateral (RUL) treatment at variable dosage can produce seizures of equal duration to bilateral treatment. With low levels electrical stimulation, RUL patients showed only 17% improvement inHAM-D scores compared to 70% in the BL group, despite the same mean seizure duration.[22]

Positioning electrodes over the non-dominant hemisphere causes lesssevere cognitive side effects than bilateral placement.[11,24] In spite of extensive research however, the relative efficacy of right unilateraland bilateral electroconvulsive therapy is controversial.[2,34,35] There are studies which have found superior efficacy with bilateral therapy,[22,36,37] and then there are other studies which have reported equivalent efficacy.[38,39] Because ofthis uncertainty, the American Psychiatric Association TaskForce on Electroconvulsive Therapy recommended thatelectrode placement be determined on a case-by-case basis.[2]

Multiple ECT stimuli (MECT) is given to patients to achieve longer cumulative seizure durations. The clinical improvement in depression correlates to patients' total seizure time in MECT. But there is no proven study on the benefits of increased seizure time from the increased number of stimuli administered.[40]

Endocrine Measures

Oxytocin. According to studies, the measurement of oxytocin released from posteriorpituitary has a direct relationship with HAM-D measured improvement in depression.[41] The concentration of oxytocin-associated neurophysin (AON) serum was calculated before and after the patient's treatment of ECT. The increase in AON positively affects HAM-D. This neurophysin response was evident on ECT treatment but does not relate to EEG-measured seizure duration.

Prolactin. The surge of prolactin released during ECT treatment can be an indicator of clinical improvement. Seizure duration is associated with a rise in prolactin.[42] However, the relationship between the magnitude of prolactin release and benefits of ECT is yet to be established.[24]

Cortisol. Although several variables have been studied as a possible predictor for the efficacy of ECT but results regarding hypercortisolism have been inconsistent. There has been a study to evaluate the relation between pre-treatment cortisol levels and the efficacy of ECT in a population of drug-free inpatients with severe major depression. This study suggests that higher levels of post-dexamethasone salivary cortisol at 9 AM are predictive of ECT efficacy.[43]

Elevated glucocorticoids may increase the vulnerability of the brain to the adverse effects of repeated seizures.This hypothesis was tested in a study and it was found that, ECT treatments delivered over 2 weeks resulted in a significant improvement in mood and a decline in most measures of cognitive performance. Elevated basal cortisol was associated with a greater decline in performance of executive function, visuospatial processing speed, and verbal memory. It was concluded that elevated cortisol predicts a greater degree of ECT-induced cognitive impairment. [44]

Medication

Concurrent medication. Concurrent therapy can be considered under two headings: general medication and psychotropic medication. Both can affect seizure threshold. Anticonvulsants, hypnotics and membrane stabilisers tend to raise the seizure threshold, while preparations containing theophyllines can have the opposite effect. Concurrent psychotropic medication can have a significant effect upon ECT. Benzodiazepines are

anticonvulsant and should be avoided if possible, but it is important to remember that there are risks associated with their sudden withdrawal. Some authorities have suggested short-term reversal with flumazenil if their presence is considered to be a limiting factor in the success of ECT, but experience is limited.[45,46] Tricyclics tend to be proconvulsant, but there is little evidence of any detrimental effect on ECT. Selective serotonin reuptake inhibitors (SSRIs) tend to reduce seizure threshold and may be associated with prolonged seizures. Monoamine oxidase inhibitors increase seizure threshold and it is essential that the anaesthetist is aware that the patient is taking this class of medication or has done so within the previous 2 weeks. Lithium reduces seizure threshold and serum levels should be checked regularly and kept within a moderate range (0.4–1 mmol/l). Selective inhibitors of the reuptake of noradrenaline in common with SSRIs, can reduce seizure threshold and also cause hypertension. Neuroleptics tend to be proconvulsant at low dosage but increase seizure thresholds at higher dosage.

In a retrospective study of 455 patients involving 5482 treatments differences in tolerability and clinical effectiveness were found between combination therapy (ECT administered together with neuroleptic medication) and ECT monotherapy.[47] Seizure duration which was assessed by EEG was significantly longer in patients treated with combination therapy using neuroleptics with lower antipsychotic potency; whereas seizure duration assessed by EEG-monitoring-electromyograph (EMG) was shorter in combination treatments done with atypical substances. In a parallel study, of ECT monotherapy or combination therapy with antidepressants using the same patient group, seizure duration was unaffected by most antidepressants but SSRIs lengthened seizure activity.[48] In addition this study found that therapeutic effectiveness was significantly enhanced in the patients receiving tricyclic antidepressants, the tetracyclic antidepressant mirtazapine or SSRIs.

There may also be a role for antidepressants in the prevention of relapse following ECT. A small double-blind placebo controlled study of the tricyclic antidepressant imipramine involving 27 depressive inpatients who had failed on pharmacotherapy prior to ECT showed that imipramine, when compared to placebo, resulted in a significant decrease in the risk of relapse of patients receiving ECT.[49] This study is in broad agreement with an earlier randomized, double-blind, placebo-controlled trial using another tricyclic antidepressant nortriptyline, or combination therapy of nortriptyline with lithium in the prevention of post-ECT relapse in patients with unipolar major depression.[50] In 29 patients receiving placebo the relapse rate during the 24 week duration of the trial was 86%; whilst in 27 patients receiving nortriptyline 60% relapsed; and 39% of the 28 patients receiving nortriptyline and lithium combination therapy relapsed during the time of the study.

Other parameters

The effectiveness of the treatment is influenced by many other underlying factors, specifically the conditions and factors relating to individual patients. This would include age, sex, physical health status, co morbidities etc. Thus, one should always consider other factors that might affect the efficacy of ECT. Two recent small Japanese studies have suggested that some cardiovascular and EEG parameters may act as markers to predict the therapeutic response of ECT in depression. Posticta l systolic heart rate and blood pressure were found to be significant predictors of the therapeutic efficacy of ECT in a study of 24 patients with depression;[51] with higher systolic heart rate and blood pressure being associated with more effective ECT.

Discussion

ECT is widely used to treat certain psychiatricdisorders, particularly major depression. Although ECT has been extensively used there is little published information on the effect of seizure parameters and the effectiveness of ECT. There is evidence that supports the direct relationship of seizure duration and the effectiveness of ECT but the latest research suggests that the length in time of the cerebral seizure activity or the tonic–clonic convulsion is not related to clinical effectiveness.[10,11] The effectiveness of ECT is related to the quality of cerebral seizure activity and cannot simply be related to its length in time alone. One of the important parameters in predicting clinical response is the degree to which electrical stimulus exceeds the seizure threshold.

Past research has shown that a generalized seizureof adequate duration is necessary and sufficient for antidepressanteffectsand that the intensity of the electrical stimuluscontributes to decreased cognitive function, the principal sideeffect, but not to effectiveness.[7] Different types of anaesthetics, or concurrent medications can affect the seizure parameters and its efficacy.[52,53] Research shows that a generalized seizureof adequate duration is necessary and sufficient for antidepressanteffects[1,7] and that the seizures of less than 15 seconds duration are ineffective. There are other studies which mention that seizure duration does not influence the effectiveness of the ECT.[10,11]

The Future

Clinicians need to continue to research this difficult area within psychiatry to enhance the evidence base and fill such gaps in this evidence as highlighted by the ECT Handbook.[54] On-going research is needed into what is a proven treatment of depressive illness and this should include more in depth research into the relationship of the above discussed parameters with its effectiveness.

“If ECT is ever legislated against or falls into disuse, it will not be because it is an ineffective or dangerous treatment, it will be

because of a failure to supervise and monitor it correctly"[55] and such supervision includes future quality research by concerned clinicians. Current NICE guidelines have limited the use of ECT to individuals with severe depressive illness, catatonia or a prolonged or severe manic episode who have been unresponsive to other treatment options.In addition, intervention of ECT should be considered to be short term and NICE does not recommend using it as maintenance therapy.[56] As research into ECT develops, the consequences may be an even more targeted approach to the use of ECT as therapy.

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