Exciting matters in electroconvulsive therapy : studies on seizure thresholds

Waarde, J.A.. van

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Retrospective study of continuation electroconvulsive therapy in 50 patients

Jeroen A. van Waarde
Dianne Wielaard
Jaap Wijkstra
Bastiaan Verwey
Rose C. van der Mast

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Abstract

Background: To examine patient and treatment characteristics in continuation electroconvulsive therapy (c-ECT), defined as prolonged treatment with ECT with a maximum frequency of once a week to prevent relapse.

Methods: Medical charts of 50 patients (mean age, 59 years; 74% were female) undergoing c-ECT were examined retrospectively for patient and treatment characteristics. Electrical stimulus dosage, seizure duration, and post-ictal suppression indices between the first and the last 4 ECT sessions were compared, and their associations with the time interval between c-ECT sessions were analyzed.

Results: Almost all patients (n=46; 92%) experienced recurrent medication-resistant mood disorders. During a median c-ECT period of 393 days (interquartile rate, 211-677 days), the frequency of c-ECT ranged from once a week (n=15; 30%) to once every 4 to 6 weeks (n=17; 34%), and ECT was administered almost exclusively bifrontotemporally (n=46, 92%). The mean time interval between consecutive c-ECT sessions was 19 (SD ± 11) days. The number of days between c-ECT sessions correlated positively with median seizure duration (motor activity: r=0.390, P=0.005; electroencephalographic activity: r=0.351, P=0.013).

Conclusions: In 50 patients with long-standing, recurrent, medication-resistant mood disorders who were treated with c-ECT, increased time interval between consecutive c-ECT sessions was correlated with increased seizure duration. Whether bifrontotemporal c-ECT requires a lower frequency to sustain remission compared with unilateral c-ECT needs further investigation.

Introduction

In patients with depression, electroconvulsive therapy (ECT) is effective in the short term, but without further prophylactic treatment, relapse rates are high.[1] In some highly medication-resistant patients, continuation ECT (c-ECT) is the only treatment option for lasting relief of severe depression and for prevention of relapse.[2,3] The cumulative probability of survival without relapse or recurrence of depression at 5 years was 73% for patients treated with c-ECT and 18% for patients treated with antidepressants alone.[4] Others found a modest effectiveness for c-ECT that was comparable to continuation pharmacotherapy in preventing relapse of depression and superior in effectiveness compared to a historical placebo control group.[5]

To provide effective ECT, the charge needed to elicit a seizure must exceed the seizure threshold and, in right unilateral electrode placement, be even substantially more (e.g., 6-12 times) than the seizure threshold.[6] Because the seizure threshold seems to increase during a course of ECT (albeit not in all patients), it is suggested to make adjustments towards higher electrical stimulation during the ECT course.[2,7] Seizure duration, however, was shown to decrease during a course, even after administration of higher electrical stimuli.[8-10] According to the anticonvulsant hypothesis of the mechanisms of action of ECT, increase of seizure threshold and decrease of seizure duration may be markers of anticonvulsant brain processes that are thought to promote and sustain remission of depression.[11] They may, however, also be the outcome of changes in brain neurophysiology that accompany remission.[11] For example, compared to nonresponders, responders to ECT had a larger seizure threshold increase during the course,[10,11] although not consistently.[12,13] Seizure threshold seemed to return to previous baseline values within a few weeks to months after completing ECT.[11,14,15]

When the time interval between ECT sessions exceeded 60 days, seizure durations were shown to increase again, which corresponds to the decrease of the seizure threshold or loss of anticonvulsive action of ECT.[8] Furthermore, in case of a rapid decrease of seizure threshold with greater spacing of the c-ECT sessions, electrical dosage might be in excess of what is needed to sustain remission, because the dosages used at the end of the index ECT are often continued in c-ECT.[11] However, others reported no increase in seizure duration with an increase in time interval during c-ECT.[16]

Research on c-ECT is sparse, and the time interval between sessions seems important for management of c-ECT. Therefore, this retrospective cohort study examines possible correlates of the time interval between c-ECT sessions on the

one hand and patients' and treatment characteristics, such as seizure duration and the amount of post-ictal suppression (PIS) on the electroencephalography (EEG), on the other. As also suggested by others,[10] we hypothesized that the longer the time interval between c-ECT sessions (*a*) the longer the seizure duration and (*b*) the smaller the amount of PIS.

Methods

Subjects

During the period 1997 to June 2009, all patients treated with c-ECT at the Rijnstate Hospital (a 600-bed general teaching hospital; n=18) and the University Medical Center Utrecht (n=32; 1,042 beds) were included in the study. We defined c-ECT as treatment with ECT at a maximum frequency of once a week to sustain remission of depression, following an index ECT course of twice a week. The patients' characteristics (sex, age, psychiatric diagnosis, length of illness before index ECT, severity of depression, and severity of somatic comorbidity) were retrieved from their medical records. Psychiatric diagnosis, as assessed by experienced psychiatrists, was classified according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.[17] Depression severity was measured using the Hamilton Depression Rating Scale (HDRS).[18] The HDRS at the start of the index ECT and at the end of the c-ECT (or the last available HDRS of the c-ECT period) were used. The severity of somatic comorbidity was assessed using the modified Cumulative Illness Rating Scale (CIRS).[19]

Data on the initial 4 sessions of the index ECT and the last 4 sessions of the c-ECT were collected from the patient medical records. The initial seizure threshold was recorded, if present, in milliCoulombs (mC). From the first and the last 4 ECT sessions, the mean electrical stimulus dosage in mC, the median dosage of the used anesthetic (in milligrams [mg]), the median of seizure duration (measured as motor activity at the cuffed limb, and seizure activity on the EEG, in seconds [s]), and the median of PIS (in percentage [%]) were calculated. Furthermore, the time interval between consecutive c-ECT sessions, the number of previous sessions, and the electrode placement (right unilateral according to d'Elia or bifrontotemporal) were noted.

ECT and measurement of seizure threshold

ECT was administered using the Thymatron IV (Somatics Incorporation, Lake Bluff, Illinois, USA), after induction of anesthesia intravenously with etomidate (1.5 mg/kg body mass) or methohexital sodium (1-1.5 mg/kg) and muscle paralysis

with succinylcholine (0.5-1 mg/kg body mass) intravenously and with appropriate oxygenation (100% oxygen, positive pressure) until the resumption of spontaneous respiration. EEG parameters were recorded and calculated by the Thymatron IV device, which provided the PIS in %.

The initial seizure threshold at the first ECT session was measured by an empirical titration method according to the guidelines of the American Psychiatric Association.[3] If the starting stimulus dose failed to elicit a seizure of at least 20 seconds' duration measured with the cuff method, stimulus charge was increased according to the titration schedule (for patients aged < 50 years: 5%, 10%, 20%, 40%, and 80%; for patients aged ≥ 50 years: 10%, 20%, 40%, and 80%), and the patient was restimulated after 30 seconds. At the second session, the dosage was set at 2.5-times seizure threshold for bifrontotemporal treatment and at 6-times seizure threshold for unilateral treatment. Dosage was adjusted during the course of the ECT to maintain seizure duration of at least 20 seconds as measured with the cuff method. The patients were treated twice weekly. The experienced clinicians decided to reduce the treatment frequency when a maximum response had been reached or a plateau in response occurred. First, ECT was administered once a week, followed by once in 2 weeks, once in 3 weeks, and so on, and each reduction in frequency was based on clinical judgments.[3] When patients showed signs of relapse, after reevaluation of the psychiatric diagnosis and other treatment options, the ECT frequency was increased and tapered when a plateau was reached again.

Statistical analysis

Data were analyzed using SPSS for Windows, version 15 (SPSS Inc., Chicago, Illinois, USA), calculating frequencies and percentages for categorical variables, and mean and standard deviation (SD) values or median values and interquartile rates (IQRs) for continuous variables. Furthermore, from the first 4 index ECT sessions and the last 4 c-ECT-sessions, the mean (± SD) used electrical stimulus dosage, and the median and IQR of the seizure duration and the PIS were calculated. Data of the 4 sessions were used to prevent influence of single outliers or missing data.

For comparison of the first 4 and the last 4 ECT sessions, paired t-tests were used for normally distributed continuous variables (mean of the first and last 4 electrical stimuli) and Wilcoxon signed rank tests were used for nonnormally distributed continuous variables (median of the first and last 4 seizure durations, PIS values, and dosage of anesthetics). Possible correlations between the first index ECT sessions and the last c-ECT-sessions and between the time interval of consecutive c-ECT sessions on the one hand and patients' and treatment characteristics on the other were calculated using Pearsons' correlation coefficients, and Spearman's rho

in case of nonnormally distributed variables. The time interval of right unilateral c-ECT (n=4) was compared with that of the bifrontotemporal c-ECT (n=46) with the Mann-Whitney U-test. Level of significance was $P \leq 0.05$.

Results

Patients' characteristics

The demographic and clinical characteristics of the 50 patients are summarized in Table 1. Most patients were female (n=37; 74%) and the mean age (± SD) was 59 ± 14 years. Almost all patients (n=46; 92%) were experiencing a medication-resistant mood disorder, mostly recurrent (n=43; 86%). The median illness duration was 10 years (IQR, 4-18.5 years). The mean HDRS at the start of the index ECT was 23 ± 8 points (n=30) and 10 ± 7 points at the last c-ECT sessions or end of treatment (n=29; paired t-test=5.542; *df*=26; *P*<0.0001). The mean CIRS score regarding somatic comorbidity remained unchanged.

Treatment characteristics

Table 2 summarizes the treatment characteristics of the 50 patients treated with c-ECT. Most of them were treated with ambulatory c-ECT (n=47; 94%). The ECT was administered mostly bifrontotemporally (n=46; 92%), and in most cases, methohexital (n=29; 58%) or etomidate (n=19; 38%) were used as an anesthetic. Dosages of anesthetics at the first and last 4 sessions showed no significant differences. The median initial seizure threshold, which was measured in 40 patients, was 63 mC (IQR, 49-151 mC).

The mean time intervals between the 2 ECT sessions were 19 ± 11 days; in the bifrontotemporal c-ECT a median of 20 days (IQR, 7-28 days; n=46), and in right unilateral c-ECT a median of 14 days (IQR, 7-26.5 days; n=4; Mann Whitney U-test=81.000; Z=-0.395; *P*=0.72). At the last 4 c-ECT-sessions, 15 patients (30%) were treated once a week and 17 patients (34%) with time intervals exceeding once every three weeks. A median of 28 (IQR, 16-59) ECT sessions was administered during a median c-ECT period of 393 days (IQR, 211-676 days).

Comparison of first index ECT and last c-ECT sessions and their correlations

Table 3 shows that at the start of the index ECT, the mean values of the mean values of electrical stimulus dosage were 167.3 ± 120.6 mC and 360.7 ± 255.9 mC in the first 4 and last 4 c-ECT sessions, respectively. These mean values differed significantly (paired t-test -5.479; *df*=49; *P*<0.001) and also correlated significantly

Table 1 Characteristics of patients (n=50) treated with continuation electroconvulsive therapy (c-ECT)*

Sex	
Male	13 (26)
Female	37 (74)
Current age, mean ± standard deviation (SD); range, in years	59.3 ± 14.2; 20-85
Psychiatric diagnosis	
Depressive disorder, recurrent, severe without psychotic features	33 (67)
Depressive disorder, recurrent, severe with psychotic features	10 (20)
Bipolar I disorder, last episode depressive	3 (6)
Schizoaffective disorder, bipolar type	2 (4)
Bipolar II disorder	1 (2)
Not described	1 (2)
Psychotic features present	13 (26)
Severity of depressive symptoms according to the HDRS[$]	
at start of the index ECT, mean ± SD (n=30)	23.0 ± 8.2[¶]
at study entrance or at end of c-ECT treatment (n=29)	10.1 ± 6.9[¶]
Duration of disease before index ECT, median; IQR[#], in years	10; 4-18.5
Severity of somatic comorbidity at start of the index ECT, measured with CIRS[$$], mean ± SD (n=47)	21.0 ± 2.6
Indication for continuation ECT	
Psychopharmacological drugs resistant	46 (94)
Psychopharmacological drugs contraindicated	2 (4)
Patients' preference	1 (2)
Not described	1 (2)

*Data are presented in numbers with percentages unless otherwise specified; [#]Interquartile range; [$]Hamilton Depression Rating Scale is a validated, observer-rated scale to measure severity and change of depressive symptoms, ranging from 0-54;[¶]Paired t-test=5.542; d*f*=26; *P*<0.0001; [$$]Modified Cumulative Illness Rating Scale is a validated, observer-rated scale to measure severity of illnesses, ranging from 14-70.

and positively (Pearson's correlation coefficient, 0.287; *P*=0.043). In the first 4 index ECT sessions, the median values of the median values of motor and EEG seizure activity duration were 36 seconds (IQR, 32-49 seconds) and 59 seconds (IQR, 44-73 seconds), respectively. In the last 4 c-ECT-sessions, the median values of the median values of motor and EEG seizure activity duration were 38 seconds (IQR, 28-47 seconds) and 52 seconds (IQR, 40-66 seconds), respectively. These median values between the first 4 and last 4 sessions did not differ significantly, but the median of EEG duration in the first 4 sessions correlated significantly and positively with

Table 2 Treatment characteristics of patients (n=50) treated with continuation ECT (c-ECT) *

Type of ECT, duration and treatment setting:	
Mean number of days between two c-ECT sessions ± SD#	19.3 ± 11.2
in right unilateral c-ECT (n=4)	15.8 ± 10.5
in bifrontotemporal c-ECT (n=46)	19.6 ± 11.4
Total number of c-ECT sessions, median; IQR#	27.5; 15.8-58.5
Duration of c-ECT period, median; IQR, in days	393; 211-676
ECT provided ambulatory	47 (94)
Characteristics of c-ECT and anesthesia:	
Bifrontotemporal electrode placement	46 (92)
Right unilateral electrode placement according to d' Elia	4 (8)
Initial seizure threshold (n=40), median; IQR, in mC#	63; 48.9-151.1
Use of etomidate, median dose and IQR, in mg#	19 (39); 20; 18-20¶
Use of methohexital, median dose and IQR, in mg	29 (59); 105; 72.5-127.5¶¶
Use of propofol, median dose and IQR, in mg	1 (2); 20; 20-20
Most recent frequency of c-ECT:	
Once a week	15 (30)
Once every two weeks	9 (18)
Once every three weeks	9 (18)
Once every four weeks	10 (20)
Once every five weeks	5 (10)
Once every six weeks	2 (4)

*Data are presented in numbers with percentages unless otherwise specified; #IQR=Interquartile range; SD=standard deviation; mC=milliCoulombs; mg= milligrams; ¶Median dose of etomidate at index-ECT was 20 mg (IQR, 19-20 mg); Wilcoxon Signed Ranks test revealed no difference compared with dose at c-ECT, Z=-1.394, *P*=0.16; ¶¶Median dose of methohexital at index-ECT was 110 mg (IQR, 78.8-150 mg); Wilcoxon Signed Ranks test revealed no difference compared with dose at c-ECT, Z=-0.631, *P*=0.53.

the median EEG duration in the last 4 sessions (Spearman *r*=0.294, *P*=0.043). The median values of the PIS of the first 4 (90%; IQR, 85-95%) and the last 4 (94%; IQR, 89-96%) sessions differed significantly (Wilcoxon signed ranks test; Z=-2.327; *P*=0.02) and were also significantly and positively correlated (Spearman *r*=0.470; *P*=0.001).

Correlation of the time interval between consecutive ECT sessions and patients' and treatment characteristics

A higher number of days between c-ECT sessions correlated moderately but significantly with increased median duration of motor seizure activity (Spearman *r*=0.390; *P*=0.005) and with increased median duration of EEG seizure activity (Spearman *r*=0.351; *P*=0.013) as assessed during the last 4 c-ECT sessions (Figure 1).

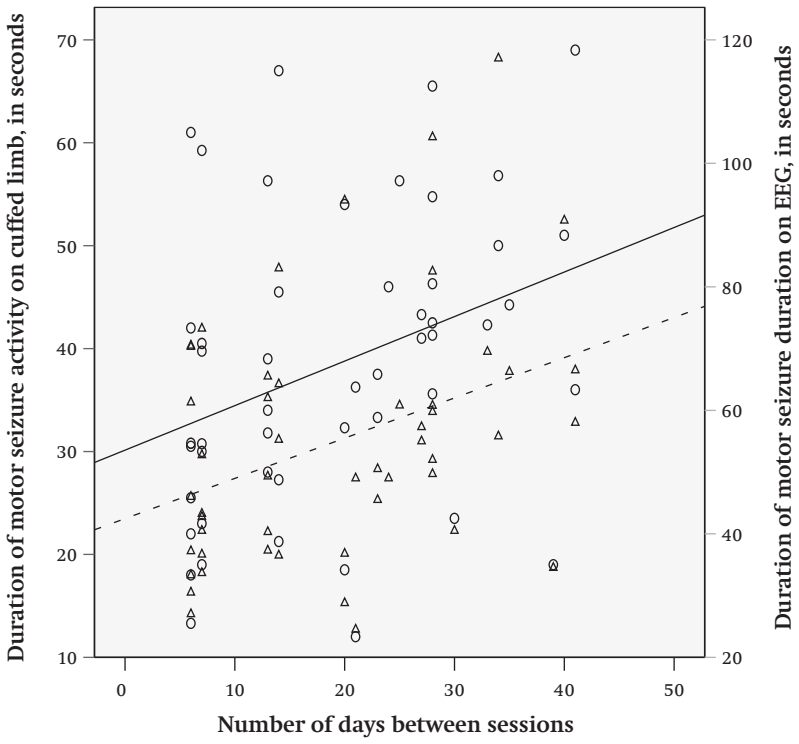
Table 3 Comparison of treatment characteristics in 50 patients treated with electroconvulsive therapy (ECT), calculated from the first 4 index ECT sessions and the last 4 continuation (c-ECT) sessions, and their correlations

	At first 4 index ECT sessions	At last 4 c-ECT sessions
Mean stimulus dose ± SD* of, in mC*	167.3 ± 120.6#	360.7 ± 255.9#
Median duration of motor seizure activity; IQR*, in seconds	35.5; 32-49.3†	38.3; 27.8-47.2†
Median duration of EEG seizure activity; IQR, in seconds	58.9; 44.1-72.6††	52.4; 39.6-65.7††
Median post-ictal suppression index, in %; IQR	90; 85-94.5¶	94.0; 89.4-95.9¶

*IQR=Interquartile range; SD=standard deviation; mC=milliCoulombs; #paired t=-5.479; d*f*=49; *P*<0.0001; higher used electrical dosages at index ECT correlated with higher dosage at c-ECT, Pearson's correlation coefficient 0.287; *P*=0.043; †Wilcoxon Signed Ranks Test showed no significant difference, *P*=0.589; no significant correlations between duration of motor seizure activity between index ECT and c-ECT, Spearman *r*=0.263, *P*=0.074; ††Wilcoxon Signed Ranks Test showed no significant difference, *P*=0.589; longer duration of EEG seizure activity at index ECT correlated with longer EEG seizure activity duration at c-ECT, Spearman *r*=0.294, *P*=0.043; ¶Wilcoxon Signed Ranks Test: Z=-2.327; *P*=0.02; higher PIS at index ECT correlated with higher PIS at c-ECT, Spearman *r*=0.470; *P*=0.001.

The median PIS of the last c-ECT sessions showed no significant correlation with the time interval (Spearman *r*= -2.39; *P*=0.095). Higher patient age correlated moderately with higher initial seizure thresholds (Spearman *r*=0.504; *P*=0.001), with increased mean of the used electrical dosage of the last 4 c-ECT sessions (Pearson *r*=0.301; *P*=0.033) but not significantly with the median values of motor or EEG seizure duration.

Figure 1 Correlation time interval and seizure activity



Discussion

In this retrospective study among 50 patients who were treated with c-ECT, the frequency of c-ECT ranged from once a week to once every 4 to 6 weeks, whereas the mean time interval between consecutive c-ECT sessions was 19 days. A median of 28 ECT sessions was administered during the entire c-ECT period of a median of 393 days. Compared with the baseline, the HDRS scores seemed to be decreased in c-ECT, which indicates the ability of c-ECT to sustain remission of depression. The electrical stimulus dosage increased significantly between the start of the index ECT and the 4 last sessions of c-ECT, and higher electrical dosage at index ECT was associated with higher electrical dosage administered in c-ECT. In addition, an increased time interval between consecutive c-ECT sessions correlated moderately with increased seizure duration but not with PIS, a parameter for seizure adequacy in ECT.

The association we found between increased seizure duration and increased time interval of c-ECT is in accordance with another study that showed increased seizure duration when time intervals exceeded 60 days; the latter authors suggested that the increase of seizure duration was a sign of decreased seizure threshold or loss of anticonvulsive action.[8] In our study, however, seizure duration increased when the time interval was less than 60 days.

In a comparable retrospective study among 41 patients (mean age, 63 years; 76% were female) undergoing c-ECT predominantly because of a mood disorder, patients were treated almost exclusively with right unilateral c-ECT; the time interval of treatments was mostly once every 2 weeks (n=10), and no patient was treated less than once every 3 weeks.[20] In our study, the patients were almost exclusively treated bifrontotemporally, the median time interval was 20 days, and 17 patients (34%) were treated with time intervals longer than once every 3 weeks. These differences might signify that the optimal time interval in bifrontotemporal c-ECT is longer compared to right unilateral c-ECT.

Seizure threshold increase is greater in bilateral index ECT than with unilateral ECT,[21] and it has been suggested that seizure threshold would rapidly decline with greater spacing of c-ECT-sessions.[11] In the present study, it was not possible to verify this decline because we did not measure seizure thresholds during the c-ECT period. Therefore, we cannot exclude that the electrical dosage was in excess of that which was needed to sustain remission. For this reason, some authors suggest repeated measurements of seizure threshold during ECT,[11] particularly after 2 months of treatment.[8]

Because our study was retrospective, the results must be interpreted with caution, as various confounders (such as concomitant medication use or substance abuse) might have influenced seizure thresholds, electrical stimulus dosage used, seizure duration, and PIS. In addition, because patients' electrical stimulus dosage during index-ECT and c-ECT was individualized and did not follow standard protocols, the increased electrical dosage at c-ECT is difficult to interpret.

In conclusion, in the present study, electrical stimulus dosage in c-ECT was higher compared with index ECT. An increased time interval between consecutive c-ECT sessions correlated moderately with increased motor and EEG seizure duration, possibly indicating a decrease of seizure threshold or loss of anticonvulsive action when time intervals between c-ECT sessions increase. Further research is needed to determine whether bifrontotemporal c-ECT requires a lower frequency to sustain remission compared to unilateral c-ECT.

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