

## Follow-up Study on Electroconvulsive Therapy in Treatment-resistant Depressed Patients after Remission: A Chart Review

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**Objective:** Electroconvulsive therapy (ECT) has proven to be effective in treatment-resistant depression (TRD). In recent reports, 70% to 90% of patients with TRD responded to ECT. However, post-ECT relapse is a significant problem. There are no studies investigating risk factors associated with reintroducing ECT in depressive patients after remission previously achieved with former ECT. The aim of the present study is to examine such risk factors using a sample of TRD patients.

**Methods:** We conducted a chart review to examine patient outcomes and adverse events over short- and long-term periods. Forty-two patients met the criteria for major depressive disorder.

**Results:** The response rate was 85.7% (36/42). There were no significant differences in the baseline characteristics of patients exhibiting remission, response or non-response. The rate of adverse events was 21.4% (9/42). Among 34 patients who were available for follow-up, 18 patients relapsed (relapse rate, 52.9%), and 6 patients were reintroduced to ECT. The patients' age and age of onset were significantly higher in the re-ECT group than non re-ECT group.

**Conclusion:** Our results suggest that older age and older age of onset might be considered for requirement of re-ECT after remission previously achieved with former ECT.

**KEY WORDS:** Electroconvulsive therapy; Treatment resistant depression; Aging; Drug therapy.

### INTRODUCTION

Electroconvulsive therapy (ECT) has proven effective in the treatment of major depressive disorder<sup>1)</sup> and especially treatment-resistant depression (TRD).<sup>2,3)</sup> Several recent reports have shown that 70% to 90% of patients with TRD responded to ECT.<sup>4-7)</sup> Though the short-term efficacy of ECT is reported to be high, relapse rates are also high.<sup>8-10)</sup> Therefore, maintenance and continuation of ECT for a period of roughly 6 months has been recommended.<sup>11,12)</sup> According to the guidelines for ECT published in the United Kingdom by the National Institute for Health and Clinical Excellence, the long-term benefits and risks of maintenance ECT have not been clearly established. In a clinical setting, antidepressants can be administered on a short-term basis after initial ECT

treatment. However, once patients have relapsed or experienced recurring depressive episodes after the first ECT session, reintroduction of ECT should be considered. Although ECT is generally considered a safe procedure, no existing research has investigated the risks and benefits associated with reintroducing ECT. In this study, we conducted a chart review to examine the short-term effects and adverse events associated with ECT, the long-term effects after 1 year, and the factors involved in reintroducing ECT for patients exhibiting TRD.

### METHODS

A systematic chart review was conducted at the Department of Psychiatry, School of Medicine, University of Occupational and Environmental Health (UOEH), Japan. ECT was conducted in the psychiatric ward of the University hospital from January 2005 to December 2010 for 56 patients who had been diagnosed with major depressive disorder (F32 or F33 according to the International Classification of Disease, 10th edition). TRD was defined as a failure to respond to adequate trials of 2 dis-

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tinctly different classes of antidepressants (stage II definition from Thase and Rush<sup>13</sup>). The recorded patient information included age, sex, number of past admissions, duration of illness and current episode, time to relapse or recurrence, time to readmission, past and current suicide attempts, presence of psychotic symptoms and the number of ECT sessions. A patient's outcome was measured 1 year after the final ECT treatment was given.

Forty-four of 56 patients with TRD were diagnosed with major depressive disorder, and data from 42 of the 44 patients (F32=10; F33=32) were included, as 2 patients did not complete the ECT treatment course. Background information on the subjects is presented in Table 1. The antidepressants used and number of subjects treated with each were paroxetine (n=9), sertraline (n=8), mirtazapine (n=5), milnacipran (n=4), duloxetine (n=4), fluvoxamine (n=1), and other medications (n=11).

A physical examination, blood and urine examinations, electrocardiogram, cerebral computed tomography scan and chest film were used to assess each patient's general medical condition. Each subject received premedication including atropine sulfate (0.5 mg i.v.), propofol (1.0 mg/kg i.v.), vecuronium (0.5-1.0 mg i.v.) and succinylcholine (1.0 mg/kg i.v.). ECT was performed between 7:00 and 9:00 AM using a Thymatron TM DG (Somatics Inc., Lake Bluff, IL, USA) with standard settings<sup>14</sup> and a brief bipolar square wave pulse. The patients were given bilateral ECT with two stimulus electrodes placed over the left and right frontotemporal scalp. ECT conditions

were identical for all patients (maximum charge delivered 504 mC, current 0.9 A, frequency 10-70 Hz, pulse width 0.5 ms, maximum duration 8 s). Motor convulsions, electroencephalograms, induced tachycardia and electromyograms were monitored during ECT as necessary. ECT was administered 12 times (three times a week for four weeks). Patients were placed on drug treatment for at least one week before ECT, and drug treatment was maintained during the entire study period. After ECT, patients were seen in outpatient setting.

Depressive symptoms were clinically evaluated using scores on the 17-item version of the Hamilton Rating Scale for Depression (HAM-D-17)<sup>15</sup> before and after ECT treatment. Each attending psychiatrist for each patients assessed HAM-D-17 within a week after final ECT. Remission was defined as a HAM-D-17 score below 7, and response was defined as a final HAM-D-17 score improvement of at least 50% compared to baseline. We also defined relapse or recurrence of depressive state as HAM-D-17 scores of 15 or more.

The Mann-Whitney U-test and Fisher's exact test were used to statistically compare the measured variables of 2 groups, and Tukey's *post-hoc* tests were used in conjunction with analysis of variance (ANOVA) to compare the measured variables of 3 groups. A result was considered to be statistically significant at  $p \leq 0.05$ . This study was approved by the Institutional Review Board at UOEH and was exempted from the requirement for informed consent because the study involved deidentified data acquired during routine care.

## RESULTS

Twenty-three patients (54.8%) experienced a remission, 13 exhibited a response to treatment, and 6 presented non-response. The overall response rate (including remissions) was 85.7%. There were no significant differences in the baseline characteristics of the remission, response and non-response groups (Table 2). Nine patients (21.4%) experienced adverse events, including delirium (n=5), amnesia (n=2), headache (n=1) and galactopoiesis (n=1) during continuation ECT.

We were able to follow up on 34 patients 1 year after ECT treatment (8 patients went to other department) and found that 12 patients were stable, 18 patients (52.9%) had relapsed and 4 patients (11.8%) had experienced a recurrence. All patients continued only antidepressant treatment with sertraline (n=8), mirtazapine (n=7), paroxetine (n=5), duloxetine (n=5), milnacipran (n=3), fluvox-

**Table 1.** Background of subjects (n=42)

| Characteristic                                 | Data                |
|--|---------------------|
| Age (year)                                     | 61.3±13.6 (27-81)   |
| Gender   | 6 (38.1)            |
| Male   | 26 (61.9)           |
| Female   |                     |
| Diagnosis (ICD-10)                             |                     |
| F32  | 10                  |
| F33  | 32                  |
| Duration of illness (year)                     | 7.4±8.9             |
| Age at onset (year)                            | 53.3±16.3           |
| Duration of current episode (month)            | 9.7±10.7            |
| HAMD-17 at start                               | 21.9±5.9            |
| Patients with psychotic symptoms               | 13 (31.0)           |
| History of past suicide attempts               | 8 (19.1)            |
| Number of past administrations                 | 1.2±1.0             |
| Number of ECT                                  | 10.5±2.8            |
| Dose of antidepressant (imipramine equivalent) | 130.2±58.8 (10-225) |

Values are presented as mean±standard deviation (range), or number (%). ICD-10, International Classification of Disease, 10th edition; HAM-D-17, Hamilton Rating Scale for Depression; ECT, electroconvulsive therapy.

**Table 2.** Differences in clinical course

| Characteristic                       | Remission | Responders | Non-responders | p value            |
|--------------------------------------|-----------|------------|----------------|--------------------|
| Patients                             | 23        | 13         | 6              |                    |
| Age (year)                           | 57.8±14.7 | 66.8±12.1  | 62.7±11.8      | 0.169*             |
| Percentage of males                  | 43.8      | 31.3       | 25.0           | 0.247 <sup>†</sup> |
| Duration of illness (year)           | 6.7±5.3   | 8.4±13.8   | 7.8±8.0        | 0.853*             |
| Age at onset (year)                  | 51.3±14.9 | 56.1±19.7  | 55.0±14.7      | 0.690*             |
| Duration of current episode (month)  | 9.4±11.2  | 9.8±9.8    | 10.3±12.8      | 0.984*             |
| HAMD-17 at start                     | 20.6±5.9  | 25.0±6.0   | 20.0±3.0       | 0.068*             |
| Patients with psychotic symptoms (%) | 69.2      | 30.7       | 0              | 0.214 <sup>†</sup> |
| Number of past administrations       | 1.2±1.0   | 1.1±1.0    | 1.5±1.2        | 0.703*             |

Values are presented as number or mean±standard deviation. \*By analysis of variance (ANOVA), *post-hoc* Tukey. <sup>†</sup>Fisher's exact test, *post-hoc* Tukey. HAMD-17, Hamilton Rating Scale for Depression.

**Table 3.** Comparison among patients with and without reintroduction of ECT

|  | Re-ECT     | Non re-ECT | p value                           |
|--|------------|------------|-----------------------------------|
| Patients                                       | 6          | 16         |                                   |
| Age (year)                                     | 74.5±4.8   | 60.4±12.5  | 0.015* <sup>†</sup>               |
| Percentage of males                            | 16.7       | 31.3       | 0.634 <sup>†</sup>                |
| Duration of illness (year)                     | 4.2±6.8    | 8.2±10.8   | 0.086*                            |
| Age at onset (year)                            | 70.3±9.2   | 50.3±14.8  | 0.009* <sup>†</sup>               |
| Duration of current episode (month)            | 5.0±3.0    | 8.6±9.6    | 0.738*                            |
| HAMD-17 at start                               | 22.0±2.3   | 22.1±6.0   | 0.971*                            |
| Patients with psychotic symptoms (%)           | 16.7       | 25.0       | 1.000 <sup>†</sup>                |
| Number of past administrations                 | 0.8±0.8    | 1.3±1.1    | 0.421*                            |
| Time to readmission (month)                    | 6.0±2.2    | 2.8±2.7    | 0.061*                            |
| Time to relapse or recurrence (month)          | 4.2±2.7    | 1.6±1.2    | 0.023 <sup>†</sup> , <sup>‡</sup> |
| Dose of antidepressant (Imipramine equivalent) | 154.2±62.1 | 143.8±49.4 | 0.868*                            |

\*Mann-Whitney U test, <sup>†</sup>Fisher's exact test, <sup>‡</sup> $p \leq 0.05$ . ECT, electroconvulsive therapy; HAMD-17, Hamilton Rating Scale for Depression.

amine (n=2) or other medications (n=4). Six patients (5 patients were relapsed and 1 was recurrence) were reintroduced to ECT. All 6 patients with TRD were diagnosed with major depressive disorder (relapsed or recurrence), and they had not been conducted the ECT until these times. We compared the background factors of the patients who were reintroduced to ECT treatment (re-ECT group) and those not re-ECT (non re-ECT group) (Table 3). The mean age and age at onset of the depressive episodes of the re-ECT group were significantly higher than those of the non re-ECT group (age: re-ECT 74.5±4.8 years, non re-ECT 60.4±12.5 years,  $p=0.015$ ; age at onset: re-ECT 70.3±9.2 years, non re-ECT 50.3±14.8 years,  $p=0.009$ ). The mean times to relapse and recurrence of the re-ECT group were significantly longer than those of the non re-ECT group (re-ECT 4.2±2.7, non re-ECT 1.6±1.2,  $p=0.023$ ). The re-ECT group was treated but failed to respond to adequate trials of 2 distinctly different classes of antidepressants when they had a relapse or recurrence after the first ECT. The mean HAMD-17 scores of the re-ECT group on the 2nd time ECT were 22.8±5.4. The re-

sponse rate was 66.7%.

## DISCUSSION

The major finding of this study was that elderly patients were more prone to relapse and recurrence, suggesting that older depressed patients may exhibit a greater degree of treatment resistance. Global predictors of TRD included comorbid axis I disorders and medical illnesses such as diabetes mellitus and hypertension.<sup>16)</sup> It has been reported that ECT is more effective in older patients than in younger adult patients.<sup>17,18)</sup> Accordingly, there have been many studies of ECT of elderly patients.<sup>19,20)</sup> Older patients may tend toward ECT treatment as a result of continuation pharmacotherapy after ECT.

The response rate in patients with TRD was 85.7%, which is similar to that reported in previous studies.<sup>3,21-23)</sup> The patient demographics of the three groups (remission, response, and non-response) were not significantly different. Delirium was the most frequent adverse event with a rate of 12.5%, similar to the rate observed in a previous

study.<sup>24)</sup> Watts *et al.*<sup>25)</sup> have reported that the mortality rate of ECT is less than one death per 73,440 treatments, and the most commonly reported adverse events after ECT are injury to the mouth and problems related to paralysis. Other adverse events reported after ECT include cognitive dysfunction, delirium, memory impairment, headache and amnesia. We have also published a case report about galactopoiesis.<sup>26)</sup> Strategies developed to decrease the incidence of post-ECT relapse include continuation ECT at biweekly or monthly intervals over 4 to 6 months and continuation pharmacotherapy after ECT.<sup>27)</sup> In naturalistic follow-up studies, it has been reported that 51% of major depressive disorder patients who receive usual care with continuation antidepressants alone or in combination with lithium experienced a relapse within 6 months.<sup>28)</sup> A prospective naturalistic study found a post-ECT relapse rate of 64.3% after 6 months, with a median time to relapse of 8.6 weeks.<sup>29)</sup> The Health Technology Assessment Committee reported a relapse rate at 12 months of 33% for continuation ECT, 32% with lithium in combination with a tricyclic antidepressant, 56% with a tricyclic antidepressant and 72% without treatment.<sup>30)</sup> The reported depression relapse rates with continuation ECT and continuation pharmacotherapy are 37.1% and 31.6%, respectively.<sup>31)</sup> In this study, all subjects were treated with continuation pharmacotherapy, and the relapse rate was 52.9%. In this study, the response rate in the re-ECT group was 66.7%. To the best of our knowledge, there is no study about response rate in reintroduction of ECT. It has been however reported that maintenance ECT might be useful for prevention of relapse and recurrence in chronically depressed patients who responded to acute treatment with ECT.<sup>32)</sup> Although the 6 patients in our study did not be selected to receive continued ECT, such treatment would have been beneficial for them. Possible limitations of this study include the small sample size and the retrospective chart review approach. Large prospective studies may identify precise factors characterizing TRD patients who may benefit from a reintroduction of ECT. In conclusion, 85.7% of patients experienced a short-term response to ECT, with a 21.4% incidence of adverse events. After a 1-year period of continuation pharmacotherapy, the long-term relapse rate was 52.9%, and older patients were retreated with ECT more frequently than younger patients.

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