Effects of Stimulus Intensity on the Efficacy of Bilateral ECT in Schizophrenia: A Preliminary Study

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Background: This preliminary study examined the effects of electrical stimulus intensity on the speed of response and efficacy of bilateral electroconvulsive therapy (ECT) in the treatment of schizophrenia.

Methods: Sixty-two patients with schizophrenia received combination treatment with bilateral ECT and flufenthixol. Using a randomized, double-blind design, the effects of three dosages of the ECT electrical stimulus were examined. Patients were treated with a stimulus intensity that was just above seizure threshold, two-times threshold, or four-times threshold. Assessments of outcome used the Brief Psychiatric Rating Scale, Global Assessment of Functioning, and the Mini-Mental State Exam.

Results: Thirty-three of sixty-two patients met remitter criteria, including maintaining improvement over a 3-week stabilization period. The dosage groups were equivalent in the number of patients who met remitter criteria. The low-dose remitter group (n = 11) received more ECT treatments and required more days to meet remitter status than both the twofold (n = 11) and fourfold remitter groups (n = 11). There was no difference among the groups in change in global cognitive status as assessed by the Mini-Mental State Exam.

Conclusions: This preliminary study indicates that treatment with high-dosage bilateral ECT speeds clinical response in patients with schizophrenia. There may be a therapeutic window of stimulus intensity in impacting on the efficacy of bilateral ECT, which needs further study. A more sensitive battery of cognitive tests should be used in future research. Biol Psychiatry 2000;48:222–228 © 2000 Society of Biological Psychiatry

Key Words: Electroconvulsive therapy, method, efficacy, schizophrenia

Introduction

Since its inception, electroconvulsive therapy (ECT) has been used to treat schizophrenia. Neuroleptic medications rapidly replaced ECT after their introduction in the 1950s. During the 1970s, when limitations in the efficacy of neuroleptics and adverse effects from prolonged use were recognized, interest in ECT as a treatment for medication-resistant schizophrenia returned (Fink and Sackeim 1996). A number of surveys in several countries found that from 2.9% to 36% of patients receiving ECT had a diagnosis of schizophrenia (Krueger and Sackeim 1995). This rate was reported to be 60% and 75% in Czech (Baudis 1992) and Indian patients (Shukla 1981), respectively.

Research on the use of ECT in schizophrenia has been characterized by a variety of methodologic limitations, including uncertain diagnostic criteria, nonrandom assignment to treatment groups, and lack of blind and reliable clinical assessment (Krueger and Sackeim 1995). Nonetheless, the conclusions suggested in this literature are that 1) ECT is effective in the treatment of schizophrenia, especially among patients with acute exacerbations, relatively short duration of illness, or both; and that 2) combined ECT and neuroleptic treatment is more effective than either ECT alone or neuroleptic treatment alone (Chanpattana et al 1999a, 1999b; Fink and Sackeim 1996).

The interactive effects of stimulus intensity and electrode placement on the efficacy of ECT in major depression is established (Sackeim et al 1987a, 1987b, 1993, in press; Krystal et al 1998; McCall et al, in press). With right unilateral ECT, the likelihood of clinical response in major depression is highly dependent on the degree to which stimulus dosage exceeds seizure threshold. With both right unilateral and bilateral ECT, higher stimulus intensity results in faster clinical improvement (Nobler et al 1997; Sackeim et al 1993, in press). The impact of electrical dosage in moderating the efficacy of bilateral ECT in schizophrenia is unknown. We hypothesized that high-dosage bilateral ECT would enhance the speed of clinical response in patients with schizophrenia.
Methods and Materials

Subjects
Sixty-seven patients (30 men, 37 women) with acute psychotic exacerbations and who met the DSM-IV criteria for schizophrenia (American Psychiatric Association 1994) were referred for ECT because of failure to respond to neuroleptic treatment. Psychiatric diagnosis was based on the consensus of three psychiatrists and also had to concur with the patients’ medical records. Diagnosis in the medical records had to be consistent throughout the episode of illness. Other inclusion criteria were a minimum pretreatment score of 37 on the Brief Psychiatric Rating Scale (BPRS, 18 items, rated 0–6; Overall and Gorham 1962), and subjects had to be between ages 16 and 50 years. Patients were excluded if they received treatment with depot neuroleptics or ECT during the previous 6 months, psychotic disorders due to a general medical condition, neurologic illness, alcohol or other substance abuse, or serious medical illness. All patients had normal results of complete blood count, serum electrolytes, and electrocardiography. This study was approved by the Ethics Committee of the Faculty of Medicine of Srinakharinwirot University and the National Review Board of Research Studies in Humans of Thailand. After complete description of the study and the opportunity to ask questions, voluntary written informed consent was obtained from the patients or their guardians.

Twenty-three patients (10 men, 13 women) were randomized to receive low-dosage bilateral ECT (dose just above the seizure threshold), 23 patients (11 men and 12 women) were assigned to the twofold seizure threshold group, and 21 patients (9 men and 12 women) were assigned to the fourfold seizure threshold group. Five patients dropped out from this double-blind comparative study—two from the low-dose group, two from the twofold seizure threshold group, and one from the fourfold seizure threshold group—leaving 62 patients in the study.

Procedures
Neuroleptic medications prescribed before the study were discontinued without a washout period. Flupenthixol was started before the first ECT session and was continued throughout the study. The dosage schedule of flupenthixol was fixed at 12 mg/day (≈600 mg chlorpromazine [CPZ] equivalents) during the first week, 18 mg/day (≈900 mg CPZ equivalents) for the days 8–10, and 24 mg/day (≈1200 mg CPZ equivalents) thereafter, depending on tolerability. All patients were treated between 18–24 mg/day of flupenthixol, which has a half-life of approximately 35 hours, leading to steady state at 7 days. Benzhexol (4–15 mg/day) was used to manage extrapyramidal symptoms, with dosage titrated on a clinical basis. Diazepam (10 mg/day) was prescribed to control agitation on a PRN basis and was withheld at least 8 hours before each ECT treatment.

Electroconvulsive therapy was administered three times per week. The ECT devices were a Thymatron DGx and MECTA SR 1. Each patient was treated with only one ECT device (two different hospitals participated in the study, each using a different device). Thiopental (2–4 mg/kg) was used at the lowest dosage to induce general anesthesia, minimizing effects on seizure threshold. Succinylcholine (0.5–1 mg/kg) served as the muscle relaxant. Atropine (0.4 mg intravenously) was administered approximately 2 min before the anesthetic. Patients were oxygenated from anesthetic administration until postictal resumption of spontaneous respiration. Bitemporal bilateral electrode placement was used throughout. The tourniquet method and two channels of prefrontal electroencephalogram (EEG) were used to assess seizure duration. An adequate seizure was defined as a tonic-clonic motor convulsion occurring bilaterally for at least 30 sec, plus EEG evidence of a cerebral seizure. Reliance on the duration of motor manifestations to define adequacy was conservative because EEG ictal expression typically outlasts motor expression for several seconds (Sackeim et al 1991; Warmflash et al 1987). Grossly suprathreshold stimulation can result in reduced seizure duration, below conventional cutoffs for “adequacy” (American Psychiatric Association Task Force, in press; Sackeim et al 1991); however, it was felt that the stimulus intensities used here, all adjusted relative to initial seizure threshold, would be insufficient to result in a marked shortening of seizure duration. In each treatment one adequate seizure was elicited.

Using the empirical titration technique (Sackeim et al 1987c), seizure threshold was quantified at the first two treatment sessions and was defined as the minimal electrical stimulus (in milliarcoulombs) to produce a motor seizure duration of at least 30 sec. For the MECTA SR 1, the titration schedule followed that used by Coffey et al (1995). With the Thymatron DGx, the first stimulus at the first treatment session was 10% of total charge. If this failed to produce an adequate seizure, electrical dosage was increased in 10% steps. This approach roughly matched the charge delivered by the MECTA SR 1 and Thymatron DGx at each step in the titration schedule. There was a limit of four stimulations in a session, but the maximal number administered in this sample was three. A 40-sec interval elapsed between each step in the titration, and no patient required additional thiopental.

At the second treatment session, patients were stimulated with an intensity 5% below the first treatment’s threshold value. If this failed to produce an adequate seizure, the first session’s value was adopted as the initial seizure threshold (ST). Patients were then stimulated with the assigned electrical stimulus charge (either 1, or 2, or 4 × ST). If the decreased intensity produced an adequate seizure, this new value was taken as the ST, and there was no further stimulation in that session. At subsequent sessions in the 1 ST group, if needed, electrical stimulus dosage was increased by one step to achieve an adequate seizure. In the 2 ST and 4 ST groups, the duration of motor seizures was ignored during the three subsequent sessions. Afterward, if the seizure was shorter than 30 sec, the delivered charge was increased by one step. At the 10th treatment session, all patients were reassessed for ST. The stimulus charge was then adjusted based on the assigned ST group or to the maximal charge settings of the device.

Clinical Evaluation
The criterion for clinical response corresponded to a BPRS score of 25 or less, as described elsewhere (Chanpattana 1997). The patients who manifested this level of clinical improvement went
on to a 3-week stabilization period (Chanpattana 1998, 1999; Chanpattana et al 1999a, 1999b). The stabilization period comprised the following treatment schedule: 3 ECT treatments in the first week, then once a week for the second and third weeks (during which BPRS scores of 25 or less had to be consistently maintained). If BPRS scores rose above 25 at any time during this period, and the total number of ECT treatments was less than 20, patients returned to the acute ECT treatment regimen and repeated the acute phase and stabilization schedules again. Patients with BPRS scores above 25, who had already received 20 ECT treatments, were considered ECT nonresponders. The same considerations applied to the patients who had not shown significant improvement (BPRS > 25) until their 20th ECT treatment. Thus, ECT responders were patients who completed the 3-week stabilization period during which the BPRS score assessed before each treatment was consistently 25 or less.

Means used to assess study outcome were 1) BPRS assessed before each treatment, during the acute and stabilization periods, and end of the study (1 week after the last treatment); 2) Global Assessment of Functioning (GAF) assessed before each acute treatment and at the end of the study; and 3) the Mini-Mental State Exam (MMSE, Thai version; Kongsakon and Vanichtanom 1994) assessed at the same time as the BPRS. Three psychiatric nurses served as raters, masked to the treatment conditions. Each patient was rated by the same nurse. These raters underwent training for 12–24 months. Interrater reliability was assessed. Each rater provided ratings simultaneously on 10 patients. Each patient was interviewed by a psychiatrist for 20 min. The correlations of BPRS scores between each rater and the psychiatrist indicated strong reliability (0.93, 0.96, and 0.97).

Statistical Analyses

The results are expressed as mean ± SD. Seizure threshold data were analyzed after logarithmic transformation to improve the normality of the data distribution (Sackeim et al 1987b). For discontinuous data, chi-square tests were used to test for differences among the groups. One-way analyses of variance (ANOVA) were used to compare the three treatment groups in continuous demographic and clinical variables. Significant main effects of treatment group were followed by Scheffe post hoc comparisons to identify pair-wise differences. The groups were compared in speed of response by conducting ANOVAs on the number of ECT treatments and the number of days in ECT treatment for patients who met initial and final remitter criteria. In addition, across the total sample, Kaplan-Meier survival analyses were conducted on these measures, treating ECT nonresponders as censored observations.

Results

Sixty-seven patients with schizophrenia received ECT. Five patients dropped out, leaving 62 patients in the study. All 5 patients who dropped out withdrew consent, reporting fear of ECT, despite receiving basic information about ECT and schizophrenia. Table 1 presents demographic and clinical features of the 62 patients as a function of treatment condition. There were no significant differences among the three treatment groups in any variable. Thirty-three patients maintained remitter status through...
the stabilization period and were classified as ECT responders. There was no difference in response rate among the three treatment groups [52%, 52%, and 55% for 1 ST, 2 ST, and 4 ST, respectively; p < 0.02; 1 ST vs. 2 ST, p = 0.003; 1 ST vs. 4 ST, p < .001]. The 2 ST and 4 ST groups did not differ significantly in these measures (Table 2), although the pattern of means suggested a more rapid onset of improvement in the 4 ST relative to the 2 ST group (p = .19).

At the end of study, the same effects were manifest. Remitters in both the 2 ST and 4 ST groups received fewer treatments [F(2,30) = 18.70, p < .001; 1 ST vs. 2 ST, p < .002; 1 ST vs. 4 ST, p < .001] and had fewer days in treatment than nonresponders in the low-dosage group [F(2,30) = 16.29, p < .001; 1 ST vs. 2 ST, p = .003; 1 ST vs. 4 ST, p < .001]. The 2 ST and 4 ST groups did not differ in these measures (Table 2), although again the 4 ST group averaged three fewer treatments than did the 2 ST group (p = .13). Including the stabilization phase, remitters in the 1 ST group on average received 18.64 (SD = 4.95) treatments, whereas the 2 ST remitters averaged 12.46 (SD = 3.75) treatments and the 4 ST remitters averaged 9.18 (SD = 1.47) treatments.

These effects were reexamined using survival analysis on the total sample of 62 patients, with ECT non-responders treated as censored observations. The survival analysis on number of ECT treatments administered yielded a significant effect of treatment group [Figure 1; log-rank χ²(2) = 25.00, p < .0001], as did the analysis of the number of days in treatment [log-rank χ²(2) = 24.38, p < .0001].

The extent of clinical improvement was comparable among the three remitter groups. At the end of the study, the 1 ST, 2 ST, and 4 ST remitter groups, respectively, had 62.6%, 60.8%, and 65.6% reductions in BPRS scores and 55.5%, 66.7%, and 55.8% increases in GAF scores. In the total sample, ANOVAs were conducted on the percentage change from baseline to study exit in BPRS, GAF, and MMSE scores, with treatment group and remitter status as variables.

**Table 2. Treatment Features of Electroconvulsive Therapy (ECT) Remitters**

<table>
<thead>
<tr>
<th>Variable</th>
<th>1 ST (n = 11)</th>
<th>2 ST (n = 11)</th>
<th>4 ST (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure threshold (mC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>68.4 ± 16.1  (48–80)</td>
<td>83.2 ± 23.3  (48–128)</td>
<td>77.3 ± 29.1  (48–128)</td>
</tr>
<tr>
<td>Tenth</td>
<td>179.5 ± 97.3  (80–403)</td>
<td>222.5 ± 93.8  (126–403)</td>
<td>224 ± 55.4  (192–288)</td>
</tr>
<tr>
<td>Average charge (mC per session)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sessions 2–9</td>
<td>118.4 ± 47.1  (68–196)</td>
<td>195.6 ± 32.9  (151–259)</td>
<td>372.2 ± 66.5  (245–461)</td>
</tr>
<tr>
<td>Sessions 11–end</td>
<td>254.6 ± 131  (128–533)</td>
<td>413.1 ± 139  (230–576)</td>
<td>576 all</td>
</tr>
<tr>
<td>At first improvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of ECT treatments</td>
<td>13.6 ± 5.0   (4–18)</td>
<td>7.5 ± 3.8    (3–15)</td>
<td>4.2 ± 1.5    (3–7)</td>
</tr>
<tr>
<td>Days of treatment</td>
<td>35.4 ± 16.3  (7–58)</td>
<td>16.4 ± 11.9  (4–42)</td>
<td>7.0 ± 3.6    (4–14)</td>
</tr>
<tr>
<td>At the end of study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of ECT treatments</td>
<td>18.6 ± 5.0   (9–23)</td>
<td>12.5 ± 3.8   (8–20)</td>
<td>9.2 ± 1.5    (8–12)</td>
</tr>
<tr>
<td>Days of treatments</td>
<td>56.4 ± 16.3  (28–79)</td>
<td>37.5 ± 12.0  (25–63)</td>
<td>28.0 ± 3.6   (25–35)</td>
</tr>
</tbody>
</table>

Values are given in mean ± SD (range). mC, milliCoulombs.
*Treatment groups: 1 ST, dose just above seizure threshold (ST); 2 ST, 2 × ST; 4 ST, 4 × ST.*

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**Figure 1.** Kaplan–Meier survival plot for cumulative probability of nonresponse as a function of the number of electroconvulsive therapy (ECT) treatments. Groups were treated just above seizure threshold (1 × ST), two times above threshold (2 × ST), or four times above threshold (4 × ST).
between-subject factors. In the ANOVA on change in BPRS scores there was only a main effect of remitter status \[ F(1,56) = 102.37, p < .0001 \], Similarly, there was only a main effect of remitter status in the ANOVA on change in GAF scores \[ F(1,56) = 18.23, p < .0001 \]. This indicated that the treatment groups were equivalent in the degree of change in symptoms and functional status. The ANOVA on MMSE scores produced no significant effects, indicating that change in global cognitive status was independent of treatment condition and remitter status.

In the total sample, the three treatment groups did not differ in initial seizure threshold \[ F(2,59) = 0.40, p = .67 \] or in the percentage increase in threshold from the first to tenth treatment \[ F(2,47) = 0.79, p = .46; \text{Table 1} \]. Patients who did or did not achieve remitter status did not differ in initial seizure threshold \[ t(60) = 0.45, p = .65 \] or in the increase in threshold \[ t(48) = 0.41, p = .68 \]. Although there is some evidence that response to ECT in major depression is associated with a larger cumulative seizure threshold increase (Sackeim 1999; Sackeim et al 1987b), this does not appear to be the case in schizophrenia.

**Discussion**

This study found that speed of clinical response to bilateral ECT in patients with schizophrenia is influenced by the degree to which stimulus dosage exceeds seizure threshold. Both of the high-dosage groups had more rapid improvement than did the low-dosage group. The findings parallel the results reported in patients with major depression (Nobler et al 1997; Ottosson 1960; Robin and De Tissera 1982; Sackeim et al 1993, in press). This is of clinical importance because ECT is frequently used when rapid improvement is needed. This was the first ECT study examining the effect of stimulus intensity in patients with schizophrenia.

Dosage factors, which are known to have greater impact on the efficacy of right unilateral ECT, may also influence the therapeutic properties of bilateral ECT. In major depression, Ottosson (1960) examined the effects of stimulus dose intensity on the efficacy of bilateral ECT. Although there was no effect of dosage on response rate, speed of symptom reduction was faster in patients who received a stimulus intensity that was markedly suprathreshold. Cronholm and Ottosson (1963) reported that low-intensity, ultra-brief pulse, bilateral ECT was less effective than higher intensity, sinusoidal waveform, bilateral ECT. Robin and De Tissera (1982) found that with bilateral ECT, high-intensity brief-pulse or chopped sine wave stimulation resulting in faster clinical improvement than did low-intensity brief-pulse stimulation. Sackeim et al (1993) randomly assigned patients to four treatment conditions: low-dosage right unilateral ECT, high-dosage right unilateral ECT, low-dosage bilateral ECT, and high-dosage bilateral ECT. They found that regardless of electrode placement, the high-dosage groups had more rapid improvement than did the low-dosage groups. In addition, low-dosage right unilateral ECT had poor efficacy. In another four-group study, Sackeim et al (in press) found that markedly suprathreshold \( (6 \times ST) \) right unilateral ECT and moderate dosage \( (2.5 \times ST) \) bilateral ECT were more effective and resulted in more rapid improvement than lower intensity \( (1.5 \times ST \text{ and } 2.5 \times ST) \) right unilateral ECT. Thus, in studies of major depression, there have been repeated findings that stimulus intensity impacts on speed of clinical response. This study extends this observation to patients with schizophrenia.

Analyses restricted to the remitter sample and survival analyses of the total sample both supported the conclusion that higher stimulus intensity resulted in more rapid improvement in patients with schizophrenia. The analyses in the remitter sample were particularly critical because comparisons of speed of clinical improvement are most relevant when restricted to patients who actually respond (Laska and Siegel 1995; Nobler et al 1997). This approach also avoids confounding likelihood of response (efficacy) with speed of response (efficiency). There was no evidence in this study that the stimulus-intensity conditions differed in likelihood of response or degree of symptomatic improvement.

An unusual aspect of this study was the use of a 3-week stabilization period as a screening method to identify remitters (Chanpattana 1998, 1999; Chanpattana et al 1999a, 1999b). The stabilization period started immediately after the first sign of significant clinical improvement (BPRS \( \leq 25 \)). Stability of clinical symptoms across these 3 weeks was required for classification as an ECT remitter. Therefore, ECT remitters in this study maintained clinical improvement for a substantial period of time.

This preliminary study had a number of limitations. A washout period for previous antipsychotic medications was not used because all study patients were in psychotic exacerbations, and many patients were difficult to manage. Lack of a washout may have had a substantial effect on the patient’s initial seizure threshold because many patients had prior treatment with low potency neuroleptics (Sackeim et al 1991). In contrast, all patients were treated with flupenthixol, a typical neuroleptic with a potency about 1.5 times that of haloperidol. A fixed titration schedule of flupenthixol dosage was used to minimize variability in effects on seizure threshold.

A structured diagnostic instrument was not used. Instead, the diagnosis of schizophrenia was based on the consensus of at least three psychiatrists, which had to concur with the patients’ psychiatric records throughout
the episode of illness. Theoretically, the inclusion in the sample of patients with depressive or manic disorders could account for the concordance of the results with similar studies major depression. The relatively high representation of female patients might suggest this possibility. That the patients presented with schizophrenia is supported by the average episode duration of approximately 3.5 years (Table 1) and relatively low baseline scores on the BPRS items of depressive mood, grandiosity, and excitement, coupled with high scores on traditional BPRS positive symptoms of psychosis (data not shown).

It is well documented that ECT produces cognitive impairment (American Psychiatric Association Task Force, in press; Sackeim 1992). There were no differences among the treatment groups or among ECT responders and nonresponders in change in MMSE scores. Although this suggests that the dosage conditions did not differ in changes in global cognitive status, the MMSE is a measure insensitive to the characteristic effects of ECT on anterograde and retrograde memory (Sobin et al 1995). In major depression, there is evidence that higher stimulus intensity and longer courses of ECT treatment can result in more severe transient cognitive side effects (Sackeim 1992; Sackeim et al 1993). It will be important in future research to use more sensitive neuropsychologic measures and determine in patients with schizophrenia whether the enhancement in speed of response due to higher stimulus intensity offsets a detrimental effect of cognitive function.

In summary, this preliminary study indicates that in patients with schizophrenia, electrical dosage impacts on the speed of clinical response to bilateral ECT. Both the groups treated at twice and four times seizure threshold had more rapid improvement than did the low-dosage group, who were treated just above seizure threshold. Future research should examine the effects of high-dosage bilateral ECT on cognitive functions, which should be assessed with a comprehensive neuropsychological battery.

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