Speed of response in ultrabrief and brief pulse width right unilateral ECT

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Abstract

Ultrabrief pulse width stimulation electroconvulsive therapy (ECT) results in less cognitive side-effects than brief pulse ECT, but recent work suggests that more treatment sessions may be required to achieve similar efficacy. In this retrospective analysis of subjects pooled from three research studies, time to improvement was analysed in 150 depressed subjects who received right unilateral ECT with a brief pulse width (at five times seizure threshold) or ultrabrief pulse width (at six times seizure threshold). Multivariate Cox regression analyses compared the number of treatments required for 50% reduction in depression scores (i.e. speed of response) in these two samples. The analyses controlled for clinical, demographic and treatment variables that differed between the samples or that were found to be significant predictors of speed of response in univariate analyses. In the multivariate analysis, older age predicted faster speed of response. There was a non-significant trend for faster time to 50% improvement with brief pulse ECT (p = 0.067). Remission rates were higher after brief pulse ECT than ultrabrief pulse ECT (p = 0.007) but response rates were similar. This study, the largest of its kind reported to date, suggests that fewer treatments may be needed to attain response with brief than ultrabrief pulse ECT and that remission rates are higher with brief pulse ECT. Further research with a larger randomized and blinded study is recommended.

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Key words: ECT, predictors, pulsewidth, remission, speed of response.

Introduction

As electroconvulsive therapy (ECT) is highly efficacious and has a rapid speed of response, it is an extremely effective and essential alternative treatment for pharmacotherapy-resistant and severe depressive illness (APA, 2001; Scott, 2004; UK ECT Review, 2003). The main deterrent for its use in clinical practice is the continuing concern that it will cause memory and cognitive side-effects for some patients (Sackeim et al. 2007). There have been several strategies proposed for minimization of these side-effects (MacPherson & Loo, 2008; Pigot et al. 2008; Prudic, 2008). One approach, which has been shown to result in markedly fewer cognitive side-effects, involves a shortening of the pulse width of the ECT stimulus to what is referred to as the ultrabrief range (0.3 ms). Several studies have shown markedly reduced and even no measurable cognitive impairment after a course of ultrabrief pulse width ECT, with efficacy comparable to that of brief (0.5–1.5 ms) pulse ECT (Loo et al. 2007, 2008, 2012; Quante et al. 2011; Roepke et al. 2011; Sackeim et al. 2008; Sienaert et al. 2009, 2010).

Recently, the efficacy of ultrabrief pulse ECT relative to brief pulse ECT has been questioned. Although overall response and remission rates did not differ significantly between ultrabrief and brief pulse right unilateral (RUL) ECT (Loo et al. 2008; Niemantsverdriet et al. 2011; Sackeim et al. 2008), some studies reported that courses of ultrabrief pulse ECT required more treatment sessions, indicating a slower speed of response (Loo et al. 2008; Niemantsverdriet et al. 2011). In an earlier prospective study (Loo et al. 2008), an analysis of change in depression scores across the treatment course found a significant difference between brief and ultrabrief pulse ECT groups, when the number of ECT treatments was entered as a covariate. It is important to note that the number of ECT sessions received in these three studies was determined clinically by the treating psychiatrist responsible...
for the patient’s care rather than according to set criteria (Loo et al. 2008; Niemantsverdriet et al. 2011). The only trial that involved a randomized, controlled design, and where the length of the treatment course was determined by formal rating scale scores, according to preset criteria, included only 44 subjects. In this study, the number of treatments required did not differ between brief and ultrabrief RUL groups (Sackeim et al. 2008).

Thus, the speed of response with ultrabrief compared to brief pulse ECT is uncertain. This is a clinically significant question as ultrabrief pulse stimulation is one of the most important advances in ECT technique to date. Furthermore, ultrabrief pulse ECT is rapidly being introduced into clinical practice and information on the expected speed of response is needed to guide clinical decision making. This retrospective analysis of data pooled from three prospective studies aimed to analyse the time to improvement in depressed patients who received brief or ultrabrief pulse RUL ECT. The outcome examined was the number of treatments required for 50% improvement from baseline depression scores.

Method

Subjects

Subjects were 150 in-patients prescribed ECT by their treating psychiatrists at two hospitals in Australia: the Northside Clinic; Wesley Hospital Kogarah. All subjects were involved in the same three research studies conducted as multisite studies across these two hospitals and fulfilled the following inclusion criteria: aged at least 18 yr; met DSM-IV criteria for a major depressive episode, for which they were prescribed an acute course of ECT; had not received ECT in the past 3 months; had no drug or alcohol abuse in the last 6 months; were able to give informed consent; did not have a diagnosis of rapid cycling bipolar disorder; had no past or current neurological illness or injury. The sample for this study comprised all subjects who had received brief pulse RUL ECT at five times seizure threshold (ST) or ultrabrief pulse RUL ECT at six times ST in three research trials: a non-randomized, prospective, single-blind effectiveness trial comparing types of ECT, including brief and ultrabrief RUL ECT (N=109; including sample reported in Loo et al. 2008; ‘Effectiveness Study’); a double-blind, randomized trial of ECT alone or ECT combined with ketamine (N=29; Loo et al. 2009; subjects from ECT alone group only included; C. Loo et al. unpublished observations; ‘Ketamine Study’); a double-blind randomized trial of ultrabrief (at eight times ST) and brief pulse (at five times ST) RUL ECT (N=12, only subjects who received brief pulse RUL were included; ‘Pulsewidth Study’). Research methodology was standardized between the two hospital sites. The primary efficacy outcome was the Montgomery–Asberg Depression Rating Scale (MADRS), rated by one of four psychologist raters trained by C.L. Subjects who had at least one complete post-baseline mood assessment were included. The research trials were approved by the Human Research Ethics Committees of the University of New South Wales and The Northside Clinic. All subjects had given informed consent for ECT treatment and participation in the research trials. Diagnoses were made according to DSM-IV criteria. Demographic and clinical characteristics of subjects from the three studies were assessed in semi-structured interviews conducted by a psychiatrist or research psychologist and are shown in Table 1, with response and remission rates for each study.

ECT treatment

Subjects were anaesthetized with either thiopentone (3–5 mg/kg) or propofol (1–2 mg/kg), followed by succinylcholine (1 mg/kg). ECT was given three times per week. RUL ECT was administered with the d’Elia:

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Table 1. Demographic, clinical and ECT treatment data for the Effectiveness Study, Ketamine Study and Pulsewidth Study samples showing numbers of participants (percentage) or means (S.D.)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Effectiveness</th>
<th>Ketamine</th>
<th>Pulsewidth</th>
<th>F</th>
<th>( \chi^2 )</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>47.13 (15.76)</td>
<td>40.62 (11.82)</td>
<td>59.08 (12.84)</td>
<td>6.618</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Gender (male)</td>
<td>45/109 (41.28%)</td>
<td>10/29 (34.48%)</td>
<td>5/12 (41.67%)</td>
<td>0.457</td>
<td>0.796</td>
<td></td>
</tr>
<tr>
<td>Current episode duration (wk)</td>
<td>64.81 (81.02)</td>
<td>37.79 (42.24)</td>
<td>61.33 (89.13)</td>
<td>1.450</td>
<td>0.283</td>
<td></td>
</tr>
<tr>
<td>Bipolar</td>
<td>33/109 (30.28%)</td>
<td>6/29 (20.69%)</td>
<td>2/12 (16.67%)</td>
<td>1.807</td>
<td>0.405</td>
<td></td>
</tr>
<tr>
<td>Psychotic</td>
<td>20/109 (18.35%)</td>
<td>0/29 (0.00%)</td>
<td>0/12 (0.00%)</td>
<td>8.680</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td>Number of antidepressants failed (current episode)</td>
<td>2.50 (1.92)</td>
<td>2.14 (2.17)</td>
<td>2.10 (0.74)</td>
<td>0.538</td>
<td>0.585</td>
<td></td>
</tr>
<tr>
<td>Antidepressants taken during ECT</td>
<td>46/109 (42.20%)</td>
<td>12/29 (41.38%)</td>
<td>7/12 (58.33%)</td>
<td>1.201</td>
<td>0.548</td>
<td></td>
</tr>
<tr>
<td>MADRS pre ECT</td>
<td>34.52 (7.71)</td>
<td>32.38 (7.83)</td>
<td>31.83 (7.21)</td>
<td>1.356</td>
<td>0.261</td>
<td></td>
</tr>
<tr>
<td>Response*</td>
<td>58/67 (86.57%)</td>
<td>19/25 (75.00%)</td>
<td>8/10 (80.00%)</td>
<td>1.552</td>
<td>0.460</td>
<td></td>
</tr>
<tr>
<td>Remission*</td>
<td>29/67 (43.28%)</td>
<td>13/25 (52.00%)</td>
<td>5/10 (50.00%)</td>
<td>0.625</td>
<td>0.731</td>
<td></td>
</tr>
</tbody>
</table>

ECT, Electroconvulsive therapy; MADRS, Montgomery–Asberg Depression Rating Scale.

*In participants who had at least eight ECT or who responded/remitted prior to eight treatments.
placement of electrodes. For brief pulse RUL ECT, pulse width was 1.0 ms. For ultrabrief pulse RUL ECT, pulse width was 0.3 ms for doses up to 576 milliCoulombs (mC), but doses above this (maximum possible dose 1075.2 mC) required increments of pulse widths up to 0.7 ms in order to achieve sufficient charge. For each subject, ST was established by titration at the first ECT session. Subsequent ECT treatments were given at 5 rST (brief RUL ECT) or 6 rST (ultrabrief pulse RUL ECT). ECT dose increases were permitted over the treatment course if there was a decline in EEG seizure quality or if retitration of ST indicated changes in the threshold. Decisions to cease ECT or switch to bilateral electrode placement (due to inadequate mood improvement) were at the discretion of the clinical treating psychiatrist. Only data from RUL ECT, prior to any switch to other forms of ECT, were analysed in this study.

Mood outcomes
Severity of subjects’ depression was assessed at baseline by a trained psychologist using MADRS. Further MADRS assessments were conducted weekly and after the final RUL ECT treatment.

Data analysis
Demographic, clinical and treatment differences between subjects receiving brief pulse ECT and those receiving ultrabrief pulse ECT at baseline were examined using Pearson’s χ² tests for categorical variables and independent samples t tests for dimensional variables (see Table 2). Subjects who continued to receive ECT treatment after response continued to receive weekly MADRS ratings until the end of their course of RUL ECT to detect remission. The proportion of subjects who met criteria for response (>50% reduction in MADRS from baseline) or remission (MADRS score <10 at final rating) either before their eighth ECT or who had at least eight ECT treatments prior to final MADRS rating or censorship were examined between brief and ultrabrief ECT samples with a Pearson’s χ² test.

Number of ECT treatments prior to 50% reductions in MADRS scores, relative to baseline MADRS score, were analysed with Cox regression. As MADRS assessments were not conducted after every single ECT treatment, data on time of response were based on the principle that outcomes observed at any assessment would be carried forward to subsequent ECT treatments until a new assessment was conducted. Subjects who did not present the outcome of interest (response) at end-point of their RUL ECT course, and those where this information is not known, are censored observations. Censored outcomes were entered with the number of ECT treatments prior to the final MADRS assessment entered as the time value. Differences in proportions of cases censored between samples and in proportions of subjects who switched electrode placements prior to 50% improvement were examined with Pearson’s χ² tests.

Univariate Cox regression analyses were conducted to assess the influence of gender, age, current depressive episode duration, bipolar depression, psychosis, number of failed antidepressant medication trials during the current depressive episode (defined as ≥4 wk at adequate dose prior to commencement of ECT), concurrent antidepressant medication during ECT, study (Effectiveness, Ketamine or Pulsewidth), type of ECT (brief or ultrabrief)
and baseline MADRS score on time to 50% improvement. These variables were chosen as they have been shown in previous studies to predict response to ECT (Birkenhager et al. 2003; Coryell & Zimmerman, 1984; Daly et al. 2001; Dombrovski et al. 2005; Kho et al. 2004, 2005; Loo et al. 2011; Petrides et al. 2001; Prudic et al. 1996; Sackeim et al. 2009). Gender, bipolar depression, psychosis, concurrent antidepressant medication during ECT, study and type of ECT were entered as categorical covariates. The influence of changes in electrical dose over the course of ECT on time to improvement were analysed with univariate Cox regression analyses allowing for a time-dependent covariate. To account for the number of treatment sessions given at each dose level, the time-dependent covariate was calculated as the cumulative electrical dose after each ECT treatment [i.e. the sum of the electrical doses preceding and including the dose administered at each treatment (mcC)] with each dose calculated as:

\[
\text{Dose} \times 100 \\
\text{Initial full treatment dose}
\]

such that initial full dose for each subject was transformed to 100 regardless of ECT type or ST and all subsequent doses were expressed as a percentage of that initial dose.

Covariates were then included in the multivariate Cox regression analyses if they were found to be predictors of 50% improvement in univariate Cox regression analyses at the \( p < 0.1 \) level or, for demographic, clinical and treatment variables, if they differed between brief and ultrabrief ECT samples at the \( p < 0.1 \) level. The variable ‘study’ was included as a covariate to control for the fact that subjects had been recruited from studies of different design. Type of ECT was included in the multivariate Cox regression analysis, regardless of its significance as a univariate predictor, as this was the chief variable of interest. Hazard ratios (HR) and their 95% confidence intervals (CI) are reported for univariate and multivariate Cox regressions.

Results

Clinical, demographic and treatment differences between study samples and ECT samples

When comparing clinical and demographic variables between the different study samples, it was found that those in the Pulsewidth Study were significantly older than in the other studies (see Table 1). The Effectiveness Study sample also had a higher tendency to have psychotic features. There were no significant differences between the study samples in 50% response or remission. No other variables showed significant differences between the study samples. Baseline and treatment differences between the subjects who received ultrabrief and brief pulse ECT are shown in Table 2. More subjects in the ultrabrief ECT sample than in the brief ECT sample had dose increases over the ECT treatment course and these increases were significantly higher in the ultrabrief ECT sample (see Table 2). The brief ECT sample was significantly older than the ultrabrief ECT sample. Other variables examined did not significantly differ between the two ECT samples.

The proportion of responders and remitters among subjects who either achieved the relevant criterion prior to their eighth treatment or who received at least eight treatments are shown in Table 2. The brief ECT sample was significantly more likely to attain remission than the ultrabrief ECT sample. However, there was no significant difference in the proportion of responders between types of ECT.

Univariate analyses of time to 50% improvement

Univariate Cox regression analyses revealed age to be a significant predictor of time to 50% reduction of MADRS score from baseline (HR = 1.019, CI 1.005–1.032 \( p = 0.007 \)). Because median age was 45.5 yr, Fig. 1a shows survival curves for subjects aged 18–45 yr and for those aged 46–91 yr. Examination of this figure shows that older subjects responded faster than younger subjects. There was also a non-significant trend for lesser time to 50% improvement with brief pulse ECT (HR = 1.482, CI 0.930–2.362, \( p = 0.098 \); see Fig. 1b). Other variables analysed were cumulative dose (HR = 1.000, CI 1.000–1.001, \( p = 0.432 \)), bipolar depression (HR = 1.467, CI 0.923–2.331, \( p = 0.105 \)), gender (male; HR = 0.935, CI 0.640–1.448, \( p = 0.764 \)), current depressive episode duration (HR = 1.000, CI 0.997–1.003, \( p = 0.913 \)), psychosis (HR = 0.790, CI 0.408–1.531, \( p = 0.485 \)), number of failed antidepressant medications during current depressive episode (HR = 0.924, CI 0.817–1.045, \( p = 0.209 \)), study (Effectiveness HR = 1.018, CI 0.482–2.148, \( p = 0.963 \); Ketamine HR = 0.982, CI 0.428–2.252, \( p = 0.966 \); both samples referenced to ultrabrief study sample), concurrent antidepressant medication during ECT (HR = 0.731, CI 0.469–1.140, \( p = 0.167 \)) and baseline MADRS score (HR = 1.006, CI 0.980–1.034, \( p = 0.640 \)).

Multivariate analysis of time to 50% improvement

Multivariate Cox regression analysis of time to 50% improvement included age, cumulative electrical dose, study and type of ECT as covariates. Age was found to be the only significant predictor, with an increase in probability of reaching 50% reduction in MADRS more quickly increasing with each year of age (HR = 1.016, CI 1.001–1.030, \( p = 0.031 \)).

There was a non-significant trend for type of ECT to predict a faster time to 50% improvement (HR = 1.701, CI 0.964–3.003, \( p = 0.067 \)). Thus, at any stage of the course of ECT prior to response, subjects receiving brief pulse ECT were 70.1% more likely to achieve 50% improvement than ultrabrief pulse ECT subjects after the subsequent treatment. Cumulative electrical
There was a significant difference in rates of placement switching before 50% response ($\chi^2 = 9.835, p = 0.002$). In the brief ECT sample, 4/40 (10.00%) subjects switched to bilateral ECT prior to 50% response, while in the ultrabrief ECT sample 40/110 (36.36%) subjects switched to bilateral ECT before a 50% response was observed. The number of RUL ECT treatments did not differ significantly ($t = 0.401, p = 0.690$) between the brief ECT sample (mean = 8.25, s.d. = 3.202) and the ultrabrief ECT sample (mean = 7.58, s.d. = 3.210) in those switched prior to achieving 50% improvement.

**Discussion**

This study found that the speed of response, as measured by the number of ECT treatments required to attain 50% improvement in depression scores, may be faster for brief pulse ECT, although results differed at a trend level only. In addition, the overall proportion of subjects showing 50% response was similar for these two types of ECT, but there was a significant trend for ultrabrief ECT to result in a lower rate of remission. Taken together, these findings support suggestions from our earlier report that overall efficacy may be slightly reduced when the pulse width is shortened (Loo et al. 2008).

The main aim of the study was to examine difference in time to improvement between ultrabrief and brief pulse ECT. Other variables were entered in the analyses to control for their effects. The analyses found that older age was associated with faster improvement. Similar findings have previously been reported in the literature, although not consistently (Birkenhager et al. 2003; Damm et al. 2010; de Vreede et al. 2005; Kho et al. 2005; Kindler et al. 1991; O’Connor et al. 2001; Okazaki et al. 2010).

There are several important limitations and considerations in interpreting these results. The major limitation is that subjects for this analysis were drawn from three separate research studies and it is possible that treatment expectations, which may affect the speed of response, differed between subjects who were in an effectiveness trial where they were not blinded to the type of treatment given; subjects who were in a trial where they were randomized to receive ketamine or placebo in addition to ECT on a blinded basis, although they were not blinded to the type of ECT given; subjects in a double blind, randomized trial, where they were blinded to the type of ECT given. It is reassuring that rates of response and remission did not differ significantly between these three studies, suggesting that this was not a major contributing factor. Moreover, the multivariate analysis controlled for the factor of study. Nevertheless, differences in speed of response, which emerged at a trend level, may have been more clearly demonstrated in a larger sample drawn from a single study. Another limitation arises from the fact that treatment factors such as the presence of concurrent medications and increases in ECT dose were determined by clinical judgement rather

**Fig. 1.** Rate of 50% improvement in all subjects, grouped by (a) age and (b) electroconvulsive therapy (ECT) type.
than rigid criteria; although our analyses controlled statistically for these factors. Likewise, the decision to prescribe brief or ultrabrief pulse ECT was made by the subjects’ own clinical treating psychiatrists and results may have been biased because the psychiatrists’ decision was influenced by specific characteristics of individual subjects. A randomized design would have controlled for this. It is possible that results would have been different if the analysis was restricted to subjects who had had an adequate course of RUL ECT, with a minimum of, say, 10 treatments (e.g. as in Kellner et al. 2010). However, the rates of censorship did not differ between the treatment samples. A final limitation arose from the fact that MADRS assessments were conducted after every three ECT sessions rather than after each session. Response outcome data were therefore based on the assumption that response outcomes occurred when they were first measured, although they may have occurred earlier. MADRS assessment after every treatment in every subject may have allowed the temporal resolution necessary to detect further significant effects and/or may have modified the effects that were detected.

In conclusion, this is the largest sample in which time to response for ultrabrief compared to brief pulse ECT has been formally analysed. The results suggest that speed of response, as well as overall remission rates, are superior in brief pulse ECT. However, these findings should not be considered conclusive, given the methodological limitations discussed.

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Statement of Interest

In the last 3 years, Dr Loo has received honoraria from Astra Zeneca and Pfizer as a plenary speaker at ECT Forums supported by them.

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