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Research report

Randomized comparison of ultra-brief bifrontal and unilateral electroconvulsive therapy for major depression: Clinical efficacy

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ABSTRACT

Background: It has been suggested that electroconvulsive therapy (ECT) with an ultra-brief pulse width in combination with a bilateral electrode placement has diminished antidepressive efficacy, as compared to unilateral ultra-brief pulse ECT.
Objective: The antidepressive efficacy of bifrontal and right unilateral ultra-brief pulse (0.3 ms) ECT were compared.
Method: Eighty-one patients with a medication refractory depressive episode were treated with a course of bifrontal ultra-brief pulse ECT at 1.5 times seizure threshold or unilateral ultra-brief pulse ECT at 6 times seizure threshold by random assignment. The 17 item-Hamilton Rating Scale for Depression (HRSD), Beck Depression Inventory, Clinical Global Impression and Patient Global Impression were administered at baseline and repeated weekly during and 1 and 6 weeks after the course, by a blinded rater.
Results: 64/81 patients (79%) completed the study, half of which were treated with bifrontal ECT. At the end of the course, 78.1% of the BF group and 78.1% of the UL group responded, whereas, 34.38% ($N=11$) of the BF group and 43.75% ($N=14$) of the UL group achieved strict remission criteria (HRSD-score ≤ 7). There were no significant differences between the patients given bifrontal ECT and those given unilateral ECT, although patients receiving unilateral ECT achieved response/remission-criteria after a smaller number of treatments.
Limitations: Relatively small number of subjects.
Conclusions: Using an ultra-brief pulse width, both BF and UL-ECT are efficacious, although patients receiving UL-ECT achieve response/remission-criteria after a smaller number of treatments.
Trial registry: http://www.controlled-trials.com/
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1. Introduction

Electroconvulsive therapy (ECT) is a powerful acute treatment for severe and resistant depression (UK ECT Review Group, 2003). Since its introduction in 1938, the technique of ECT has changed considerably (Loo et al., 2006). In an ongoing attempt to improve efficacy while minimizing side-effects, both different electrode placements and stimulus parameters have been studied.

The traditional bitemporal electrode placement is very efficacious, but can induce problematic cognitive side-effects (Sackeim et al., 1993). Unilateral (UL) ECT produces less cognitive side-effects, but is also less efficacious, when used with the same stimulus dose as bitemporal ECT. Thus, with UL ECT, a

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higher stimulus dose is required (Sackeim et al., 2000). Bifrontal (BF) ECT has been proposed as a potential candidate to become the placement of first choice (Abrams, 2002), in view of the fact that it exhibits an equal antidepressant efficacy than bitemporal ECT (Bailine et al., 2000), and has few cognitive side-effects (Ranjkesh et al., 2005). Therefore, BF ECT has been adopted by clinicians striving to optimize the efficacy/side-effect profile of ECT (Loo et al., 2006).

Modern ECT-devices no longer deliver a sine wave but a square wave brief pulse stimulus. An unresolved issue in the use of brief pulse stimulation concerns the optimal pulse width (American Psychiatric Association, 2001). From neurophysiologic observations, a pulse width of 0.1–0.2 ms is optimal for neuronal depolarization (Ranck, 1975). It has been suggested that the use of a stimulus with an ultra brief (UB) pulse width, i.e. 0.3 ms, is substantially more efficient in seizure induction, thus needing less energy (Hyrman, 1999; Sackeim et al., 1994). Therefore it is supposed to produce less cognitive side-effects than standard pulse width (i.e. 0.5–2 ms) stimulation (Kim et al., 2007; Sackeim, 2004; Sackeim et al., 2008). Early research showed less retrograde amnesia with UB ECT as compared to brief pulse or sine wave ECT (Cronholm and Ottosson, 1963a; Valentine et al., 1964). In a recent retrospective study, UB UL ECT incurred less cognitive side effects than standard pulse UL ECT (Loo et al., 2007). In contrast, Pisvejc et al. (1998), in patients with schizophrenia, reported therapeutic and cognitive results of UB ECT similar to those obtained with standard pulse width ECT.

There has been a concern, however, of lower antidepressant efficacy of UB ECT, with patients needing additional treatment sessions (Cronholm and Ottosson, 1963b; Loo et al., 2007; Robin and De Tissera, 1982). Moreover, it has been suggested that the diminished antidepressive efficacy is encountered solely with the combination of an ultra-brief pulse width and bilateral, i.e. bitemporal, electrode placement, as compared to unilateral UB ECT or standard pulse ECT (Kim et al., 2007; Sackeim et al., 2008). These intriguing findings call for further study (Coffey, 2008; Lerer and Isserles, 2008). This study was set up to compare the efficacy of BF-ECT and UL-ECT in patients with a major depressive episode, using an ultra brief pulse width.

2. Methods

2.1. Study population

Patients with DSM-IV-defined major depressive disorder, either bipolar or unipolar, with or without psychotic symptoms, with an age of 18 years or older, who were referred for ECT and who had a minimum baseline score of 18 on the 17-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960) were eligible for study inclusion. Exclusion criteria included schizophrenia, neurological illness, cognitive disorder, substance abuse or dependence within the previous year, or ECT within the past 6 months. Patients provided written informed consent, and the study was approved by the Ethical Committee of the Catholic University of Leuven.

2.2. Treatment

Patients were withdrawn from antidepressants at least 3 days before starting ECT. Lorazepam up to 4 mg/day or clothiapine up to 40 mg/day was allowed if needed for agitation or anxiety. The patients received BF or UL ECT by random assignment. Anesthetic medications consisted of glycopyrrolate (0.2 mg), methohexital (1.0 mg/kg) or etomidate (0.2 mg/kg), and succinylcholine (1.0 mg/kg), all given intravenously. For BF placement, each electrode was placed 5 cm above the outer angle of the orbit on a line parallel to the sagittal plane (Letemendia et al., 1993). The d'Elia placement was used in UL-ECT (D'Elia, 1970). Treatment was given two times a week with a square-wave, brief-pulse, constant-current device (MECTA SR1 5000Q; Lake Oswego, OR, U.S.A.). At the first treatment, the subject's seizure threshold (ST) was established by empirical titration. Subsequent treatments were given at 1.5 times the ST for BF placements, and 6 times the ST for UL placements. Stimulus train duration was the longest, stimulus frequency the lowest allowed for the dose selected. Motor seizure duration was monitored with the cuff technique, and two channels of EEG (frontal-mastoid) were recorded. Patients not achieving response or remitter-criteria after study completion were further treated at the discretion of the treating psychiatrist.

2.3. Evaluation of outcome

HRSD-scores and Clinical Global Impression (CGI)-scores were obtained at baseline and once every week, until response/remission, and at 1 and 6 weeks after finishing the course, by a blinded rater. Self-rated questionnaires were Beck Depression Inventory (BDI) and Patient Global Impression (PGI). No minimum or maximum number of treatments was imposed on patients who showed substantial clinical improvement. ECT was continued until patients achieved remission or had a plateau in improvement over at least two consecutive evaluations. Remission was defined according to both moderate and strict criteria. The moderate criteria (remitter 10), required a HRSD-score of $\leq$10. The strict criteria (remitter 7) required a HRSD-score of $\leq$7, which corresponds to full remission (Thase and Ninan, 2002). Response was defined as a decrease in HRSD-score of $\geq$50%. As part of a larger cognitive test battery, described elsewhere (Sienaert et al., 2008), Mini Mental State scores (MMSE) were obtained at baseline and at 1 and 6 weeks after finishing the course.

2.4. Statistical analysis

Baseline comparisons between patients given BF and UL ECT were analyzed with standard descriptive tests: chi-square tests (or exact tests) for categorical variables and *t* tests (or Wilcoxon two-sample test) for continuous variables. To examine the difference between BF and UL ECT in outcome (response, remission 10 and 7), chi-square tests were used. To examine differences between BF and UL-ECT in HRSD, BDI, CGI, and PGI scores at baseline, the last treatment, and 1 and 6 weeks after the course of the treatment, repeated measures analysis were performed with mixed effect models (Gueorguieva and Krystal, 2004). For these models, an unstructured form for the within subject-variance structure was chosen on the basis of likelihood ratio tests and information criteria (AIC). In addition, the mean number of sessions needed to meet response and remission criteria were compared between BF and UL ECT by *t*-tests. The latter analysis, however, is necessarily restricted to the group of patients who met these criteria. Therefore, also discrete time