Effects of 3 different stimulus intensities of ultrabrief stimuli in right unilateral electroconvulsive therapy in major depression: A randomized, double-blind pilot study

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ARTICLE INFO

ABSTRACT

Objective: Efficacy and cognitive outcome of ECT is depending on electrode placement, pulse width and electrical dosage. Several studies showed that high-dosage right unilateral ECT (RULECT) had a better antidepressant effects than low-dosage RULECT and less cognitive side effect than bilateral stimulation. In this prospective, randomized, double-blind trial, we examined the efficacy and cognitive side effects of RULECT with three different (high dose) stimulus intensities ($4\times$, $7\times$ and $10\times$ above the seizure threshold (ST)).

Methods: 41 patients with treatment resistant unipolar or bipolar depression were randomized to one of the three stimulation intensities. For stimulation, we used an ultrabrief pulse (0.3 ms). Primary outcome measures were reduction of the Hamilton Depression Rating Scale (HDRS), Beck Depression Inventory (BDI) and the response rate (50% reduction of the HDRS) in the three groups. For cognitive side effects, a neuropsychological test battery was assessed.

Results: All three groups responded significantly to 9 ECTs ($p < 0.005$), but there were no statistical significant differences in the response rates between the three intensity groups. Besides of the Verbal Learning Memory Recognition Test (VLMT), which showed significant impairments in the high dose intensity groups, no differences could be shown between the three study groups in all neuropsychological tests.

Conclusion: A RULECT with ultrabrief pulse stimulation and $4\times$ ST intensity is effective and from good tolerability. Higher intensity dosages seem to be associated with more cognitive side effects during a course of acute ECT treatment.

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1. Objective

Electroconvulsive therapy (ECT) is widely used to treat certain psychiatric disorders, particularly (psychopharmacotherapy-) resistant major depression. It is highly effective for treatment of Major Depression (2003). The most common and persistent adverse effect of ECT is cognitive impairment, particularly memory dysfunction, with the tendency to resolve in the first few months after discontinuation of treatment. The amnestic effects are greatest for impersonal memory compared with autobiographical memory (Lisanby et al., 2000), and, in addition, impairments of other cognitive domains like attention or executive function in patients undergoing acute ECT treatment have been observed (Ingram et al., 2008). Monitoring of cognitive side effects had turned out to be an important issue for clinicians, as they can potentially limit the course of a presumed adequate treatment trial and patients compliance within the treatment.

Regarding stimulation parameters, both efficacy and cognitive outcome of ECT is depending on electrode placement, pulse width and electrical dosage (Sackeim et al., 1993). In the past decades, modifications of stimulation parameters were examined to minimize cognitive side effects while maintaining efficacy: first, it was shown that right unilateral ECT (RULECT) is accompanied with less cognitive side effect than bilateral ECT (Sackeim et al., 2000). Second, modification of pulse form to rectangular brief pulses

and introduction of stimulation techniques with ultrabrief pulse (0.3 ms) lead to an improvement of adverse effect profile (Geddes, 1987) in comparison to a traditional brief pulse (1.5 ms) (Sackeim et al., 2008). These results were confirmed in study of Loo et al. (2008): cognitive outcomes were superior when using ultrabrief pulse stimulation, particular to the verbal memory, as well as in retrograde autobiographical memory. These findings favour ultrabrief pulse RULECT as the most tolerable form of treatment (Prudic, 2008). Third, it had been shown that the increase of stimulation intensity lead to an improvement of antidepressant efficacy, and at the same time to a worsened neurocognitive profile in a dose-dependant manner (Sackeim et al., 2000; McCall et al., 2002; Abrams et al., 1991; Sackeim et al., 1993). However, to date, studies dealing with high intensity ultrabrief ECT are lacking. Therefore, we performed a prospective, randomized, double-blind trial, in which we examined efficacy and neurocognitive tolerability of 3 different (high dose) stimulus intensities ($4\times$ ST, $7\times$ ST and $10\times$ ST).

2. Methods

2.1. Sample characteristics

Between April 2006 and January 2009, 41 inpatients between the age of 18 and 85 years with treatment resistant depression (major depressive disorder and bipolar depression according to DSM IV) with and without psychotic features and indication of ECT (defined as at least two consecutive sufficient antidepressant medications without remission) were enrolled in the study. Exclusion criteria were coarse brain disease, ECT within 6 months before study inclusion, substance abuse, and pulmonary disease. No distinction was made between right and left motor dominant patients. All patients were on psychotropic medication. To evaluate treatment adequacy and treatment resistance for the 3 groups, we used the Antidepressant Treatment History Form (ATHF) (Sackeim, 2001). In this score, number of medications, thresholds for the dosage and duration of medications are included. The university's institutional review board approved the protocol. The subjects gave written informed consent after the procedure had been fully explained.

2.2. ECT procedure

Propofol (2 mg/kg), and succinylcholine chloride (0.75 mg/kg) were the anaesthetic medications for ECT. The d'Elia placements were used for RUL ECT. 9 sessions of electroconvulsive therapy was administered, 3 times per week for 3 weeks, with a customized MECTA spectrum 5000Q device (MECTA Corp, Lake Oswego, Ore). The seizure threshold (ST) was quantified at the first treatments using the empirical titration procedure with constant 20 Hz stimulus frequency by varying train duration. To be considered adequate, minimal seizure duration was 20 s of motor or 25 s of electroencephalographic (EEG) manifestation. After determination of the seizure threshold, patients were randomly assigned in a 1:1:1 ratio to one of the 3 stimulus intensities ($4\times$ ST, $7\times$ ST or $10\times$ ST) by using a list with repetitive numbers (for treatment group 1–3). For stimulation, we used an ultrabrief pulse (0.3 ms). In cases of inadequate seizure, the stimulus dose was increased in 25% steps and patients were restimulated. Patients and investigators not involved in ECT administration were blinded to the type of ECT.

2.3. Outcome measures

To evaluate severity of depression, the following rating scales were completed at baseline and after 3, 6 and 9 ECT sessions by a blinded psychiatrist: Hamilton Depression Rating Scale (HDRS, 28 item version) (Hamilton, 1960), Montgomery and Asberg Rating Sclae (MADRS) (Montgomery and Asberg, 1979) and Young Mania Rating Scale (YMRS) (Young et al., 1978). For self-evaluation of depressive symptoms, the Beck Depression Inventory (BDI) (Beck et al., 1961) was used. The primary outcomes were the reduction of the HDRS, BDI and the response rate (defined as a 50% reduction of the HDRS-28).

2.4. Neuropsychological testing

To evaluate cognitive functioning, patients underwent a neuropsychological test battery before treatment at baseline and at the end of treatment, after 9 sessions of RULECT. Measures at the end point were performed at least 24 h but no longer than 48 h after the last treatment. Immediate and delayed verbal memory was measured by the Verbal Learning Recognition Memory Test (VLMT), a German version of the Auditory Verbal Learning Test (Helmstaedter and Durwen, 1990). The test assesses immediate memory span (VLMT, immediate), new learning (VLMT, delayed), and recognition memory (VLMT, recognition) via verbal presentation of a word list. Working memory/attention was measured by digit span from the Wechsler Memory Scale (Wechsler, 1987), a simple test which requires immediate recall of an increasing number of digits in a forward and backward condition. We only used the forward version. In addition, phonemic verbal fluency performance (word fluency) as part from the "Regensburger Wortflüssigkeits-Test" (Aschenbrenner et al., 2000) was assessed as a measure for attention and executive function. This test requires free listing of words in a semantic (e.g. animals) and phonemic category.

2.5. Statistical analysis

Simple descriptive statistics (mean, standard deviation) were obtained for patients' demographic and baseline clinical characteristics. Repeated measurements for mean improvement consisting of 9 follow-up visits were analyzed for significant temporal trends using T-test for pairwise comparisons, and due to small sample size and lack of normally distributed values, we calculated as well non-parametric analyses (Wilcoxon) that did not show different results. A p-value ≤ 0.05 was considered statistically significant; p-values were not adjusted for multiplicity of tests. Likelihood-ratio tests and non-parametric analysis of variance (Kruskal−Wallis) were calculated to test for differences between the three patient groups at baseline and to evaluate the influence of the different intensity groups on psychometric and neuropsychological variables before (baseline) and after treatment. In addition, an analysis of variance for repeated measurements was performed to consider age as covariate in the three groups.

3. Results

Of the total sample of 41 patients; 32 had recurrent Major Depressive Disorder (MDD) and 9 were diagnosed with a Bipolar Disorder. For demographic characteristics see Table 1.

The total number of patients had a mean age of 56.5 ± 13.9 years at inclusion (at a minimum age of 22 years and maximum age of 83 years) and 76.8% were women.

The three intensity groups did not significantly differ in gender ($\chi^2 = 2.623$; d$f = 2$; $p = 0.269$), family status ($\chi^2 = 9.852$; d$f = 8$; $p = 0.276$), duration of current episode ($\chi^2 = 61.115$; d$f = 48$; $p = 0.097$), number of depressive episodes ($\chi^2 = 2.036$; d$f = 2$; $p = 0.361$), ATHF-scores ($\chi^2 = 45.305$; d$f = 40$; $p = 0.260$), years of