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Brief report

Acute antidepressant effects of right unilateral ultra-brief ECT: A double-blind randomised controlled trial

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ABSTRACT

Background: Shortening the pulse width to 0.3 ms holds neurophysiological and clinical promise of making ECT safer by limiting cognitive side effects. However, the antidepressant effects of right ultra-brief unilateral ECT are under contention. In an acute ECT course, antidepressant equivalence of ultra-brief right unilateral ECT to the high-dose brief pulse right unilateral ECT was investigated.
Methods: Severely depressed patients were randomised to 1 ms-brief pulse ($n=18$) or 0.3 ms ultra-brief pulse ($n=17$) right unilateral ECT, both at high-dose (6 times threshold stimulus dose) given thrice weekly. Depression severity was measured using the Montgomery Asberg Depression Rating Scale at baseline, after 8 treatments and after the acute course of ECT.
Results: Depression severity declined equally in both groups: F (1.27,41.97)=0.31, $p=0.63$. Median time in days to remission (95%CI) was in brief pulse ECT: 26 (18.6–33.4) and ultra-brief pulse ECT:28 (17.9–38.0).
Limitation: The small sample study in the study increases the likelihood of type 2 error.
Conclusion: In severe depression, high-dose ultra-brief right unilateral ECT appears to show matching acute antidepressant response to an equally high-dose brief pulse right unilateral ECT.

1. Introduction

Electroconvulsive therapy (ECT) is still the most efficacious treatment for severe depression (Ebmeier et al., 2006) but perhaps the most clinically neglected treatments in psychiatry (Eranti and McLoughlin, 2003). Advances in ECT standards have a principal focus, which is to make ECT safer or optimal. Manipulation of electrical stimulus parameters affords a way forward in producing more optimal ECT stimulation (Peterchev et al., 2010). One such method is to shorten the pulse width. There is a neurophysiological appeal of optimal neuronal stimulation by shortening the pulse width to 0.3 ms (ultra-brief pulse width) (Geddes, 1987), which may also reduce electrical field strength generated in the brain thereby diminishing cognitive side effects (Deng et al., 2011). Recently, clinical evidence emerged in a randomised controlled trial that in right unilateral and not bilateral electrode placement, ultra-brief (0.3 ms) ECT matched the antidepressant effects of conventional longer (1.5 ms) pulse width (Sackeim et al., 2008). However this study needs replication since concurrent clinical studies, albeight uncontrolled, showed that right unilateral ultra-brief ECT is slower (Loo et al., 2007) and ineffective (McCormick et al., 2009) compared with brief pulse ECT. There is however more unequivocal evidence of lesser cognitive side effects with ultra-brief right unilateral ECT (Loo et al., 2007; Sackeim et al., 2008), which has been summarised in a recent meta-analysis (Verwijk et al., 2012). A more recent randomised controlled trial showed that ultra-brief pulse right unilateral ECT at high dose (6 times threshold) produced comparable antidepressant effects and did not cause deleterious effects on cognition when compared with standard bifrontal ECT given at 1.5 times threshold stimulus dose (Sienaert et al.,2010). Taken together the two RCT's (Sackeim et al.,2008 and Sienaert et al.,2010) indicate that ultra-brief unilateral ECT is an effective antidepressant treatment with less cognitive side effects. This study was primarily aimed at addressing a moot question whether ultra-brief (0.3 ms) right unilateral ECT produced similar antidepressant effects as compared to 6 times threshold brief pulse (1 ms) right

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unilateral ECT, which matches bilateral ECT and is associated with a lower incidence of cognitive side effects (Sackeim et al., 2000). The primary hypothesis of this study was that during the acute ECT course, both treatment groups would result in equivalent antidepressant response. The secondary hypothesis was that both groups will show the same speed to remission of depression.

2. Methods

The study was conducted in the Mood Disorders Unit—a tertiary referral unit of a psychiatric hospital in Sydney. The study was approved by the Western Sydney Local Health District Human Research Ethics Committee (08/127). All consecutive patients referred to ECT for the treatment of a major depressive episode, who provided written informed consent, were screened between November 2008 and March 2012.The following inclusion criteria were used to define the subject group: (1) age 18–65; (2) diagnosis of major depressive episode according to MINI International Neuropsychiatric Interview (MINI) (Sheehan et al.,1998); (3) no primary personality disorder (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition), substance dependence in the past 12 months (as per MINI); (4) a score of greater than 23 on the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979).Treatment resistance was noted as failure or intolerance to at least 2 distinctly different classes of antidepressants.

Following this patients were randomised to either brief pulse or ultra-brief pulse right unilateral ECT according to a computer-generated random number list. The statistician (KB) generated the random number list. Patient allocation was placed in sequential opaque envelopes that were opened in turn within the ECT suite by the psychiatrist administering at the first ECT session. In the patients file, the pulse width used was not documented. There was a team of 3 psychiatrists who were entrusted to administer the ECT for the patients in the study. The local ECT committee credentialed their technique. The rating psychiatrist (PM) was not associated with the ECT administration. The patients were told that they received right unilateral ECT but were not told about which pulse width they received. Following this patients were randomised to either 1 ms brief pulse (BP-ECT)or 0.3 ms ultra-brief pulse (UBP-ECT),right unilateral ECT. The rater (PM) and the patients were blind to the pulse width used during ECT. Uniform ECT standards were maintained for the study sample through a team of 3 psychiatrists who administered the ECT were entrusted to administer the ECT for the patients in the study. Depression severity was measured by the MADRS.

The MADRS was administered at baseline, which was 24 h before the start of the first ECT session and repeated at 24 h both after the eighth ECT session and end of the acute ECT course. While rating the patients at the time points after 8 sessions and after the end of the acute course, both the patients and the rater were invited to guess the treatment group. The end of the acute ECT was determined by the treating team as when treatment was ceased or reduced to once a week. Since the end of the acute course would vary in time from baseline, the number of days to the end of acute course was noted for each patient.

ECT was administered using the MECTA 5000Q (Lake Osvego, Ore). Right unilateral (d'Elia) electrode placement was used in all patients irrespective of their handedness. ECT was given thrice weekly. Threshold was empirically determined during the first session. Details of stimulus titration, dosimetry, anaesthetic-modification and physiological monitoring during ECT have been described in detail elsewhere (Mayur and Harris, 2011). Patients in both treatment groups (BP-ECT and UBP-ECT) received 6 times the threshold dose from session 2 onwards. Moreover, the charge rates (stimulus frequency × stimulus train length) were kept constant in both the treatment groups during both the threshold estimation and while obtaining the 6 times threshold dose. For instance: level 1 in the titration chart was set in BP-ECT at 32 mC (20 Hz, 1 s) and for UBP-ECT at 9.6 mC (20 Hz, 1 s) and the respective 6 times threshold doses were, BP-ECT=192 mC (40 Hz, 3 s) and UBP-ECT=57.6 mC (40 Hz, 3 s). Concomitant antidepressant or antipsychotic medications were not used during the acute phase of the ECT course.

Table 1
Socio-demographic and clinical parameters.

	BP-ECT ($n=18$)	UBP-ECT ($n=17$)
Age (yrs)	43 (10.99)	43.35 (11.66)
Sex (M:F)	13:5	8:9
Treatment resistant depression (Y:N)	13:5	12:5
Bipolar depression (n)	2	5
Episode duration (months)	8.33 (7.21)	7.47 (3.71)
MADRS m(SD)	40.16 (6.83)	43 (5.78)
Threshold dose (mC)	71.11 (26.44)	22.08 (8.86)*
Suprathreshold dose (mC)	426.66(158.67)	132.48(53.18)*

* $p<0.001$.

To test the primary hypothesis, the primary end point was the MADRS scores 24 h after the end of the 8th ECT session. To test the equivalence of the two groups, power was increased to 90% to minimise type 2 error. We estimated that a sample size of 17 in each group will be adequately powered for the primary outcome measure based on the minimum between group difference of mean scores of the MADRS to be 10 or greater to be clinically meaningful and when expected differences in mean being zero and the common standard deviation is 9. All statistics was done using SPSS version 20. Two-tailed tests with a significance level of 5% were used throughout. Repeated Measure Analysis of Variance (RMANOVA) was used to compute changes in depression during the acute course. Kaplan–Meier survival analysis was provided to test differences between the two groups with respect to the likelihood and speed of remission of depression. Remission of depression was defined as reduction of the MADRS scores to 10 or less.

3. Results

45 patients with severe depression were given ECT during the period of the study. 2 patients refused to consent and 3 were unable to consent given their severity. 40 patients consented were recruited and 5 patients (3 in BP-ECT and 2 in UBP-ECT) dropped out before completing 8 treatments. Three patients (2 in BP-ECT and 1 in UBP-ECT) withdrew consent for the study of which, one patient in each treatment group withdrew consent stating that they are not improving soon enough. The remaining two patients (one in each group) withdrew due to protocol violation. The sample for analysis included 35 patients. Baseline comparisons between the two treatment groups are noted in Table 1. Of note was that all the patients in the UB-ECT group were treated with 0.3 ms throughout the acute course. Also only in 5 patients (14.2%) the rater could accurately guess the treatment. None of the patients could accurately guess their treatments.

3.1. Change in depression severity:

In the RMANOVA, Mauchly's test indicated that the assumption of sphericity was violated, $X^2(2)=27.18$, $p<0.001$, therefore the degrees of freedom was corrected using the Greenhouse–Geisser