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Research report

Relapse and long-term cognitive performance after brief pulse or ultrabrief pulse right unilateral electroconvulsive therapy: A multicenter naturalistic follow up ☆

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ABSTRACT

Background: Superior cognitive functioning for electroconvulsive therapy (ECT) with right unilateral (RUL) ultrabrief pulse (UBP) stimulation compared to RUL brief pulse (BP) stimulation is not clearly established and long-term data is needed.
Methods: We conducted a prospective naturalistic follow-up of 87 inpatients from three tertiary psychiatric hospitals. Before these patients entered the follow up phase, they had participated in a RCT comparing twice weekly RUL BP (1.0 ms) with RUL UBP (0.3–0.4 ms) ECT eight times seizure threshold until remission (MADRS < 10), for a maximum of six weeks. Three and six months after the index ECT patients were monitored for relapse and cognitive performance (retrograde amnesia, semantic memory and lexical memory). We compared relapse rate and cognitive performance between RUL BP and RUL UBP stimulation.
Results: Of the 50 patients who remitted after index ECT 44 (24 BP; 20 UBP) were monitored for follow up. Relapse occurred in 25% of the BP group and in 25% of the UBP group ($\chi^2=0.00$, $p=1.0$) at three-month follow-up; whereas 43.5% of the BP group and 35% of the UBP group relapsed ($\chi^2=0.322$, $p=0.57$) at six months follow-up. Cognitive assessments (17 BP; 16 UBP) showed no significant differences between BP and UBP groups, except for an advantage for the BP group in the autobiographical incident questions at three months follow-up only ($p=0.04$; $d=0.77$).
Limitations: This study may be limited since relapse in a naturalistic follow-up can be influenced by medication and other unknown factors, like social support, medical comorbidity, and psychotherapy. The small numbers of our subgroups hamper statistical significance.
Conclusions: Patients that achieved remission after RUL BP or RUL UBP ECT showed similar relapse rates after three and six months. There was no cognitive advantage of UBP over BP ECT in follow up.
Clinical trials registration: Netherlands trial register www.trialregister.nl registration number NTR1304

1. Introduction

Electroconvulsive therapy (ECT) with right unilateral (RUL) ultrabrief pulse (UBP) stimulation is increasingly used (Kellner, 2009; van Waarde et al., 2009) because it is supposed to have a lower risk of adverse cognitive effects with equal efficacy compared to RUL brief pulse (BP) ECT. In this respect the electrical stimulus to induce a seizure is defined as BP when the pulse width is 0.5 to 2.0 ms and UBP when the pulse width is < 0.5 ms.

The evidence, however, for equal efficacy with superior cognitive functioning for ECT with RUL UBP stimulation in the short-term is rather limited.(Spaans et al., 2013a; Verwijk et al., 2012) In a recent randomized comparison between RUL BP and RUL UBP ECT we did not find differences in cognitive effects with respect to retrograde amnesia, semantic memory and lexical memory one

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week after finishing the ECT course. However, an advantage for RUL BP ECT was demonstrated in short-term efficacy, especially in the speed of remission.(Spaans et al., 2013b) Less is known about the differences in long-term effects and cognitive performance between BP and UBP ECT due to the limited number of follow up studies.(Mayur et al., 2013; Sackeim et al., 2008) Cognitive performance after RUL BP and RUL UBP ECT was studied in two RCTs which concluded that RUL UBP ECT offered an advantage over RUL BP ECT in short-term and long-term retrograde amnesia.(Mayur et al., 2013; Sackeim et al., 2008) We chose retrograde amnesia for autobiographical memory as a focus for this study being the most prominent long-term cognitive adverse effect of ECT.(Bergsholm, 2012; Fraser et al., 2008; Rose et al., 2003; Semkovska and McLoughlin, 2013; Verwijk et al., 2012)

Older and recent studies showed a relapse rate after successful brief pulse ECT of 50% within six months, despite continuation pharmacotherapy (Jelovac et al., 2013; Prudic et al., 2013). Different ECT stimulation techniques, like high or low dose BP, RUL or bilateral (BL) ECT, that resulted in remission were found unrelated to relapse (Sackeim et al., 1993). To the best of our knowledge the relapse rate after index RUL BP and RUL UBP ECT is studied in only one RCT, in which relapse was also unrelated to treatment condition (Sackeim et al., 2008).

The aim of the present study was to compare the relapse rate and long-term cognitive performance in a naturalistic follow up at three and six months after finishing a double blind randomized controlled trial (RCT) comparing RUL BP (1.0 ms) with RUL UBP (0.3 ms) ECT (Spaans et al., 2013b). Patients were followed up for relapse and cognitive performance. We hypothesized to find no differences in relapse rate. During the index phase the charge delivered with brief pulse group was significantly higher than with ultrabrief pulse. Due to a possible slower recovery, we expected to find differences in cognitive performance, with RUL UBP ECT causing less long-term cognitive side effects than RUL BP ECT.

2. Material and methods

2.1. General description

From April 2007 till March 2011 we conducted a prospective, double blind, randomized multicenter trial comparing the efficacy and cognitive side effects of RUL BP with RUL UBP ECT (Spaans et al., 2013b) (Netherlands National Trial Register number NTR1304). Patients were recruited from three different ECT centers: Parnassia (The Hague) and GGZ Delfland (Delft) in the Netherlands and the University Psychiatric Center KU Leuven, campus Kortenberg (Kortenberg) in Belgium. The present study is an open, naturalistic follow-up study starting after finishing the RCT, with assessments at three and six months after the RCT to analyze possible differences in relapse rate and cognitive performance between the RUL BP and RUL UBP groups The Institutional Review Boards of these hospitals approved the study, which was conducted according to the declaration of Helsinki.

2.2. Patient sample

All in- and outpatients of 18 years and older suffering from a major depressive disorder or bipolar depression (with or without psychosis) according to DSM-IV criteria (APA, 2000) who were referred for ECT treatment, were screened for inclusion in the study. The diagnosis of depression was confirmed by experienced psychiatrists (HPS, KK, PS, FB) using the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998; van Vliet and de Beurs, 2007). Patients with a history of schizophrenia, schizoaffective disorder or who had dementia were excluded. All eligible patients were asked to participate and baseline assessments were done after providing informed consent.

2.3. Procedure

During the RCT, patients received twice weekly RUL BP (1.0 ms) or RUL UBP (0.3–0.4 ms) ECT eight times seizure threshold until remission (MADRS < 10), for a maximum of six weeks after which they entered the present naturalistic follow-up study. Three and six months after the index ECT patients were monitored for relapse and cognitive performance (retrograde amnesia, semantic memory and lexical memory). Patients who had ECT during follow up were excluded for the analysis of cognitive functioning.

In accordance with routine clinical practice, psychotropics and somatic medications were kept on a stable dosage during ECT. Lithium was kept at plasma levels of 0.40–0.80 mmol/L. Three days prior to ECT, benzodiazepines were tapered to a maximum of 10 mg diazepam equivalents. Etomidate ($\pm$0.25 mg/kg) and succinylcholine (1–2 mg/kg) were used as anesthetic and muscle relaxant, respectively. Seizures were induced with a square-wave BP or UBP bidirectional stimulus delivered by a constant current device (spECTrum 5000 Q MECTA inc., Tualatin, Oregon, USA) and a maximum stimulus level of 1152 mC using RUL d'Elia electrode placement (d'Elia, 1970). Seizure threshold was determined using empirical dose titration. The first and successive treatment sessions were then continued with a stimulus eight times the seizure threshold.

After the end of the RCT adjustment of patients' medication was at the discretion of the treating psychiatrist. 98% of the patients were on concomitant psychotropic medication during the index ECT and most continued their medication after the treatment. If relapse occurred the preferred treatment was ECT.

2.4. Assessments

2.4.1. Clinical assessment and demographic features

Before ECT treatment started, socio-demographic and the following clinical data were collected: Age, gender, level of education, age of onset, duration of the index major depressive episode, psychosis, polarity, number of previous admissions, history of ECT treatment and the medication resistance score according to a modified Antidepressant Treatment History Form (ATHF) (Sackeim et al., 1990). The scoring system of Verhage (1964) (range 1–7; 1=less than 6 years education, 2=6 years, 3=7–8 years, 4=9 years, 5=10–14 years, 6=more than 14 years, 7=University) was used to define the subject's level of education. The number of ECTs and total charge in the index ECT were included as additional clinical data.

2.4.2. Depression severity and relapse criteria

For blind assessment of efficacy, trained nurses rated the severity of depression using the MADRS. The severity of depression was rated at baseline, weekly during the ECT course until the end of the randomized study-period, and at the three and six months follow-up assessments. Relapse was defined as readmission for depression, restart of ECT, suicide, or a MADRS score > 15 (Taylor et al., 2004).

2.4.3. Cognitive assessment

Cognitive assessment was performed by a neuropsychologist or supervised trainee neuropsychologist, who were blind for the treatment condition. The assessments were obtained within a week prior to the first ECT (T0), one week after finishing the randomized treatment course (T1) and at follow up after three months (FU1) and six months (FU2) post-ECT.

A validated test, Kopelman's Autobiographical Memory Interview (AMI) (Kopelman et al., 1990; Meeter et al., 2006) was used to assess retrograde amnesia for autobiographical memory (personal events). This interview is a reliable and standardized test to assess personal remote memory. The AMI measures personal semantic memories and autobiographical incidents from different time periods: childhood (ages 0–18), early adulthood (ages 18–30), and recent (within the past