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Unilateral ultra-brief pulse electroconvulsive therapy for depression in Parkinson's disease

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Abstract

Objectives—Electroconvulsive therapy (ECT) has demonstrated efficacy in treating core symptoms of Parkinson's disease (PD), however widespread use of ECT in PD has been limited due to concern over cognitive burden. We investigated the use of a newer ECT technology known to have fewer cognitive side effects (right unilateral (RUL) ultrabrief pulse (UBP)) for the treatment of medically-refractory psychiatric dysfunction in PD.

Materials and methods—This open label pilot study included 6 patients who were assessed in the motoric, cognitive and neuropsychiatric domains prior to and after RUL UBP ECT. Primary endpoints were changes in total score on the HAM-D-17 and GDS-30 rating scales.

Results—Patients were found to improve in motoric and psychiatric domains following RUL UBP ECT without cognitive side effects, both immediately following ECT and at 1-month follow-up.

Conclusions—This study demonstrates that RUL UBP ECT is safe, feasible and potentially efficacious in treating multiple domains of PD, including motor and mood, without clear cognitive side effects.

Keywords

Depression; electroconvulsive therapy; Parkinson's disease; ultra-brief pulse

Introduction

Parkinson's disease (PD) is the quintessential neuropsychiatric condition with motoric impairments occurring alongside common comorbidities such as depression, apathy,

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psychosis, cognitive impairment, and impulse control disorders(1) .Unfortunately, efficacious pharmacological treatment options are often limited by these neuropsychiatric symptoms (2), with medication side effects, necessitating the use of brain stimulation technologies such as electroconvulsive therapy (ECT). ECT significantly reduces mortality in patients with treatment refractory neuropsychiatric disease (3,4). Furthermore, ECT is not only effective in treating depression and psychosis in PD, but it also has a profound and long-lasting anti-Parkinsonian effect on motoric function in the range of weeks to months (5). The use of ECT in PD patients, however, has been limited due to significant cognitive side effects, particularly delirium, induced by older forms of ECT (6).

Sackheim, et al. have demonstrated that ECT utilizing an ultra-brief pulse-width targeted unilaterally to the right cerebral hemisphere is as efficacious as bilateral ECT in treating depression but with substantially reduced severity of adverse cognitive effects (7). To date no one has explored the safety and potential efficacy of this new form of ECT for the PD population. As the pathophysiology of PD-related depression may be unique (8), and given the increased cognitive burden inherent in advanced PD, it is prudent that right unilateral ultrabrief pulse (RUL UBP) ECT be evaluated in the PD population before widespread adoption of this treatment approach.

This small open-label study evaluated the safety, feasibility, and preliminary efficacy of RUL UBP ECT in 6 inpatient participants with PD and treatment-resistant depression (TRD) or psychosis or both. In concordance with the known effects of conventional ECT in PD (5), we hypothesized that patients would significantly improve in both mood and motor function with RUL UBP ECT. We also hypothesized that acute and subacute adverse cognitive effects of RUL UBP ECT would be substantially reduced in severity compared to published side effects in patients receiving conventional bilateral ECT.

Materials and Methods

Participants

Participants (N=6) were recruited from either the psychiatry clinic or the movement disorders clinic during routine appointments at the Medical University of South Carolina (MUSC). We informed participants about the risks and benefits of all treatment options, including ECT, and described the purpose and design of the study to each patient in detail; patients provided signed informed consent to participate. The institutional review board at MUSC approved this study before any study procedures began, and the study was performed in accordance with the declaration of Helsinki.

Inclusion criteria

We screened participants for major inclusion criteria in person in the clinic during their regularly scheduled appointments. Participants must have had a diagnosis of PD made by a neurologist specializing in the treatment of movement disorders and meeting UK Brain Bank Criteria (9). Participants must have had documented motor fluctuations and/or ≥4 years of diagnosed PD. Participants also were required to have either significant co-morbid depression as measured by the Geriatric Depression Scale (GDS-30) or psychosis as

measured by Clinical Global Impression Scale (CGIS). Finally, patients had to meet clinical criteria for ECT, which included either medically refractory major depression or psychosis or both.

ECT parameters and protocol

We used glycopyrrolate (0.1mg), methohexital (1.0 mg/kg), and succinylcholine (0.75 mg/kg) as the anesthetic medications, and typically administered ECT three times per week with a Somatics Thymatron system IV ECT device. We placed electrodes in standard right unilateral locations using the classic d'Elia placement(10), and used an ultrabrief pulse width (0.25 msec). We quantified the seizure threshold using the empirical titration method (11). Following the seizure threshold determination session we treated at 6 times the initial seizure threshold for all subsequent treatments. We recorded two channels of prefrontal electroencephalography (EEG coordinates FP1 and FP2) in order to determine the duration of frontal seizure. Additionally we visually determined the duration of motor seizure based on patient movement. If we observed at least 20 seconds of tonic-clonic movement or 25 seconds of electroencephalographic seizure activity, we considered the seizure to be of an adequate duration without any participants having a suboptimal seizure.

Study design and assessment scales

The raters were independent from the ECT treating physicians. Participants received a global assessment for severity of PD, psychiatric co-morbidities, and cognitive dysfunction at baseline, which included the following scales: the Unified Parkinson's Disease Rating Scale (UPDRS), Geriatric Depression Scale (GDS-30) (12), Hamilton Depression Rating Scale (HAM-D-17) for depression (12), Scale for the Assessment of Positive Symptoms (SAPS) (13), Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease (14), Scale for Suicidal Ideation (SSI) (15), Apathy Scale (AS) (16), and Montreal Cognitive Assessment (MOCA) for cognitive dysfunction (17). Patients received 2 additional global assessments after their final ECT treatment. The first occurred approximately 48 hours to 4 days after their final ECT treatment, and the second occurred 25–40 days following their final ECT treatment. This range of assessments allowed for a scheduling window. None of the participants missed appointments. Additionally, the GDS-30, and SSI were performed immediately prior to all ECT treatments.

The primary endpoint was the change in total score on the HAM-D-17 and GDS from baseline to immediately and 1 month after final ECT treatment. Secondary efficacy endpoints were response and remission rates. Response was defined as a 50% reduction in the total HAM-D-17 score compared to baseline, and remission was defined as a total score of ≤ 7. Response as per the GDS-30 was defined as a total score of ≤ 4.

Data Analysis

The primary goal of this study was to conduct a within-subjects analysis of scores before and after ECT treatment. Timepoints of interest included 1) baseline,2) after final treatment, and 3) 1 month after final treatment. For each measure of interest, the change in score from baseline to each follow-up timepoint was calculated. A last-value-carried-forward approach was used to handle missing data. Due to the small sample size, non-parametric Wilcoxon

signed rank tests were used to determine if median changes in scores were significant, and an α value of 0.10 was used to determine statistical significance.

Results

Six patients completed the study with measures taken at baseline, immediately after ECT, and 1 month after ECT. One participant was excluded from analysis because on review the subject did not meet UK brain bank criteria. Patient demographics are presented in Table 1. Patient demographics are presented in Table 1. Mean age was 69.8 years, with 7.6 mean years of Parkinson's Disease and 23.7 mean years of depression. Baseline mean scores, scores following ECT, and scores at 1-month follow-up are shown in Table 2 with pairwise comparisons indicating change between baseline and follow-up scores. Substantial and statistically significant reductions were observed in HAM-D-17 GDS-30, AS, SAPS, and UPDRS both immediately following ECT and at 1-month followup. MOCA scores significantly improved immediately following ECT; however, scores returned to baseline values at 1-month followup. Non-significant reductions were observed in SSI and QUIPS.

Discussion

This open label pilot study demonstrates that RUL UBP ECT is safe, feasible and potentially efficacious in treating multiple domains of PD, including motor and mood, without clear cognitive side effects. Specifically, we found that patients improved significantly in their mood as measured by the HRSD and GDS. The mean HRSD score of this cohort was well within the range of severe depression at baseline (>24); however, this score fell to the lowest level of mild depression (~8) immediately following ECT and then fell further into the non-depressed range (<7) at 1-month follow up (18). Similarly, patients no longer met criteria for depression under the GDS immediately after and 1 month following ECT (19). In line with these improvements in mood, we found that levels of apathy on the AS significantly improved to low, clinically insignificant levels (16). SSI levels also decreased, although not significantly in this small cohort. It is important to note that three of the 6 patients in this cohort had deep brain stimulation (DBS) electrodes implanted, which did not have any bearing of safety or tolerability.

The mechanism of ECT-induced mood improvements may be unique in PD-related depression, as the natural history of PD-related depression differs from other etiologies (20,21). Depression in PD may be responsive to dopamine agonism (22), a unique effect that could be due to a relative hypodopaminergic state within not only the motor but also the mood neurocircuitry (23). Thus, the mechanism of ECT in treating PD-related depression may be a result of increased dopamine receptor binding caused by electroconvulsive stimulation in brain regions implicated in depression such as the nucleus accumbens (24,25). It is likely that the anti-depressant mechanism of ECT is not completely unique in PD patients (26).

We observed significant improvements in psychosis following ECT. Psychosis is particularly common in patients with advanced PD who have been treated with dopaminergic agonists for long durations (27). Similarly to typical antipsychotics, ECT likely exerts its

antipsychotic effect through attenuated D2 signaling (28), as ECT has been shown to reduce D2 receptor binding in the anterior cingulate (29). Furthermore, ECT may produce an antipsychotic effect through reduced 5HT2A receptor density (30).

Significant improvements in Parkinsonian motor symptoms were observed with RUL UBP ECT, with large clinically important reductions in UPDRS scores persisting at 1-month follow up (31). This replicates results from an earlier trial of conventional bilateral ECT in patients without depression (5). ECT may improve motor symptoms in PD through the facilitation of D1 and D3 binding in the striatum (32). Additionally, ECT has been shown to increase cortical GABA concentrations (33).

We observed no deficits in cognitive functioning with RUL UBP ECT. Indeed, MOCA scores transiently increased after the ECT course was concluded and returned to baseline 1 month following ECT. We acknowledge the current study is limited by its small size and open-label design, making it more difficult to interpret any statistical inference seen at the p=0.1 level. However, preservation of cognition while significantly treating mood and motor symptoms of PD indicates a high clinical potential of RUL UBP ECT for treatment of PD. Further testing of RUL UBP ECT for PD depression or psychosis in randomized, controlled trials is warranted.

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Table 1

Patient Demographics

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Group Mean(±SD)
Gender	M	M	M	M	M	M	All
Diagnosis Recurrent	MDD	MDD	MDD	MDD	MDD	MDD	All
Age at treatment	63	70	77	60	79	66	69.8(±8.3)
Length of Parkinson's Disease (years)	5	8	15	10	7	1	7.6(±4.7)
Length of Depression (years)	29	16	33	40	14	10	23.7 (±12)
Current Depressive Episode (months)	6	8	1	30	11	60	19.3(±22.3)
Previous Brain Stimulation Therapies	Yes	No	Yes	Yes	No	No	3 Yes/3 No
Past Psychotherapy	Yes	Yes	Yes	Yes	Yes	Yes	All
Family History of Depression	Yes	Yes	Yes	Yes	Yes	No	5 Yes/ 1 No
Number of Psychiatric Treatments in Current Depressive Episode[a]	3	2	2	2	3	0	2(±1.1)
LED	16.67	300	2296.9	0	350.25	100	510.64 (±887.04)
Number of Psychotropics at Baseline	2	1	1	3	4	0	2.2 (±1.30)

M, male; MDD, major depressive disorder; LED, L-Dopa equivalent dose;

[a]Excluding psychotherapy; SD, Standard Deviation

Table 2

Scale	Baseline	Post ECT	Significance Post ECT	One Month Post ECT	Significance One Month Post ECT
HRSD[17]	34.2(±15.9) *	8.2(±10.7) *	p=0.0313	5.2(±2.2) **	p=0.0313
GDS	22.7(±4.2) *	7.8(±7.1) *	p=0.0355	4.2(±2.1) **	p=0.0355
AS	29.3(±4.7) *	9.3(±5.9) *	p=0.0355	9.4(±3.6) **	p=0.0313
SSI	3.5(±3.6) *	0.2(±0.4) *	p=0.1362	0(±0) **	p=0.1250
SAPS	15.6(±17.3) *	1.3(±3.3) *	p=0.0625	1.3(±.9) ***	p=0.0579
QUIPS	1.0(±1.7) *	0.2(±0.4) *	p=0.5000	0(±0) ***	p=0.5000
MOCA	26.3(±2.8) *	27.6(±2.6) *	p=0.0890	26.4(±3.8) **	p=0.5862
UPDRS	40.7(±15.1) *	13.2(±9.9) **	p=0.0579	19.0(±8.9) **	p=0.0625

HRSD[17], 17 Item Hamilton Rating Scale for Depression; GDS, Geriatric Depression Scale; AS, Apathy Scale; SSI, Scale of Suicidal Ideation; SAPS, Scale for Assessment of Positive Symptoms, QUIPS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; MOCA, Montreal Cognitive Assessment; UPDRS, Unified Parkinson's Disease Rating Scale.

* n=6,

** n=5,

*** n=4