Journal of Affective Disorders 222 (2017) 1–6

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Feasibility, safety, and preliminary efficacy of Low Amplitude Seizure Therapy (LAP-ST): A proof of concept clinical trial in man

Nagy A. Youssef[a,*], Emad Sidhom[b,c]

[a] Department of Psychiatry and Health Behavior, Medical College of Georgia at Augusta University, 997 St. Sebastian Way, Augusta, GA 30912, USA
[b] The Behman Hospital, Helwan, Cairo, Egypt
[c] Oxford Health NHS Foundation Trust, UK

ARTICLE INFO

Keywords:
Electroconvulsive therapy
Seizure therapy
Low Amplitude Seizure Therapy
ECT
Seizure threshold, current titration
Focal ECT
Treatment-resistant depression
Mood disorders
Psychotic disorders

ABSTRACT

Background: Current pulse amplitude used in clinical ECT may be higher than needed. Reducing pulse amplitude may improve focality of the electric field and thus cognitive adverse effects. Here we examine the feasibility, safety, and whether Low Pulse Amplitude Seizure Therapy (LAP-ST, 0.5–0.6 A) minimizes cognitive adverse effects while retaining efficacy.

Methods: Patients with treatment-resistant primary mood (depressive episodes) or psychotic disorders who were clinically indicated to undergo ECT were offered to be enrolled in an open-label study. The study consisted of a full acute course of LAP-ST under standard anesthesia and muscle relaxation. The primary outcome was feasibility of seizure induction. Clinical outcome measures were: time to reorientation (TRO), Mini Mental State Examination, Montgomery Aberg Depression Scale, and Brief Psychiatric Rating Scale, and Clinical Global Impression Scale.

Results: Twenty-two patients consented for enrollment in the study. LAP-ST was feasible, and all patients had seizures in the first session. Participants had a quick orientation with median TRO of 4.5 min. Treatment was efficacious for both depressive and psychotic symptoms.

Limitations: Relatively small sample size, non-blinded, and no randomization was performed in this initial proof of concept study.

Conclusions: This first human preliminary data of a full course of focal LAP-ST demonstrates that seizure induction is feasible. These results, although preliminary, suggest that the LAP-ST compared to the standard ECT techniques may result in less cognitive side effects, but comparable efficacy. Larger studies are needed to replicate these findings.

1. Introduction

Mood and psychotic disorders have a huge negative impact on morbidity and mortality from mental and physical illness, with a substantial burden on the health of individuals, families, and the society (Murray and Lopez, 1997; Szkultecka-Debek et al., 2016). Depression is predicted to be the second highest cause of disability after ischemic heart diseases by year 2020 (Murray and Lopez, 1997). Treatment-resistant depression (TRD) was defined by the World Psychiatric Organization and the Massachusetts General Hospital Depression Program as failure to respond to at least an adequate trial of medication (Ayd, 1983; Fava and Davidson, 1996). However, about a third of patients do not achieve remission despite 3 lines of adequate treatment trials as shown by the STAR*D clinical trial (Rush et al., 2006; Subedi et al., 2016; Szkultecka-Debek et al., 2016). ECT is used for treatment-resistant schizophrenia usually in combination with antipsychotics (Tharyan and Adams, 2005).

Electroconvulsive therapy (ECT) has been the most potent (UK ECT Review Group, 2003) and most rapid acting (Husain et al., 2004) form of intervention especially for the treatment-resistant mood and psychotic disorders in combination with medications (Griffiths et al., 2014; Kellner et al., 2016a; Levy-Rueff et al., 2008; Medda et al., 2015; Minnai et al., 2016; Palma et al., 2016; Prudic and Sackeim, 1999; Subedi et al., 2016; Tharyan and Adams, 2005; Youssef and McCall, 2014). ECT can also help prevent relapse in treatment-resistant depression with continuation ECT and medications (Kellner et al., 2016b; Youssef and McCall, 2014).

Nonetheless, cognitive and memory-related adverse effects of ECT are still a major concern. Historically, modifications in ECT parameters in the form of ultra-brief pulse instead of brief pulse (Cronholm and

* Corresponding author.
E-mail address: nyoussef@augusta.edu (N.A. Youssef).

http://dx.doi.org/10.1016/j.jad.2017.06.022
Received 8 October 2016; Received in revised form 7 May 2017; Accepted 12 June 2017
Available online 16 June 2017

Ottosson, 1963a, 1963b) and the use of rectangular instead of sine wave (Squire and Zouzounis, 1986; Weiner, 1980), as well as, right unilateral (RUL) electrode placement instead of bilateral (BL) (Squire, 1977; Squire and Slater, 1978) have lowered cognitive and memory adverse effects (Sackeim et al., 1986, 1993, 2000b, 2008). However, despite these advances, memory and cognitive side effects are still experienced by a significant proportion of patients, constitute a barrier to treatment, and may, in part, contribute to the stigma associated with ECT (Matthews et al., 2016; Sienaert, 2016). Thus, ECT is still underutilized as an effective life-saving intervention (Prudic and Sackeim, 1999), despite the fact that ECT, when indicated, has a great impact on the quality of life and functionality (McCall et al., 2013, 2011).

The current amplitude of the electric pulse is the primary factor that drives the electric field deeper in the brain structures (Peterchev et al., 2015, 2010). Thus, Low AmPlitude ECT, or more precisely Seizure Therapy (LAP-ST), should result in minimal spread of the electric field in the deeper hippocampal region and temporal lobe. (Peterchev et al., 2015, 2010). Avoidance or minimization of hippocampal and temporal lobe stimulation using LAP-ST is hypothesized to significantly reduce memory and cognitive adverse effects of ECT without affecting the more superficial stimulation of the Dorsolateral Prefrontal Cortex (DLPFC) and other cortical regions needed for the antidepressant effect (Noda et al., 2015).

Computational models of electric field induced in the brain using conventional high current amplitude is much higher than the neural activation threshold. This leads to deeper spread of the electric field in the brain. On the other hand, reducing pulse amplitude improves focality and decreases depth of penetration, thus potentially minimizing memory and cognitive adverse effects (Lee et al., 2012).

Low amplitude has been utilized in older ECT paradigms, (Friedman, 1942; Liberson, 1948) without anesthesia using older devices that have different specifications and parameters, such as being voltage constant (which leaves the current pulse amplitude to vary from patient to patient and session to session depending on the impedance). Modern ECT devices are current-constant rather than voltage-constant. This allows for true fixed current amplitude. Thus, constantly minimizing the propagation of electric fields to the deeper memory areas of the brain that is associated with the cognitive adverse effects of standard ECT. Currently, in standard clinical practice high pulse amplitude of 800–900 mA is used (Lee et al., 2016). Also, in these older studies, anesthesia was not used, which would affect the seizure threshold (ST) estimates (Avramov et al., 1995).

In modern era, seizure titration during the first session using low amplitude was successfully reported in a letter by Rosa et al., 2011 on 5 cases (Rosa et al., 2011). These case reports involved one titration session, but no suprathreshold therapeutic dose sessions using low amplitude ECT.

Nahas et al. performed a study to primarily examine investigational Focal Electrically Administered Seizure Therapy (FEAST) electrode placement and investigational unidirectional pulse (Nahas et al., 2013). In this study, low pulse amplitude were used to decrease an unusually high impedance at the smaller FEAST electrode. However, the primary aim of the study was to examine a novel electrode placement (along with a unidirectional current).

Although ECT has been in clinical practice for decades, no human studies so far primarily examined the feasibility or the effect of lower pulse amplitude of a full course on memory and cognition. Our hypothesis is that LAP-ST will reduce the cognitive burden of ECT. We also hypothesized that LAP-ST will be efficacious in both depressive and psychotic episodes. The aims of this study were to first examine the feasibility (primary outcome) of a full course of LAP-ST using low amplitude in humans and whether LAP-ST is associated with less cognitive adverse effects using Time to Orientation (as the main clinical outcome). We also explored the efficacy of LAP-ST.

2. Methods

2.1. Participants

After IRB approval, patients were offered to be enrolled in the study if they were clinically indicated to undergo ECT and had capacity to consent for the study and provided written informed consent. This study included patients with either primary mood or psychotic disorders who failed to respond to clinically adequate trials of psychopharmacological interventions in term of dosage and duration (with or without psychotherapy) as clinically indicated and were referred for ECT in The Behman hospital in Cairo, Egypt. All patients were inpatients. The Behman Hospital is a private psychiatric hospital accredited by the Royal College of Psychiatrists in England. Patients were enrolled between April 2013 to June 2015 after explanation of potential risks and any possible generalizable benefits of the study. The open-label study design involved a clinical course of LAP-ST typically given 3 times a week under standard anesthesia (sodium thiopental) and muscle relaxation (succinylcholine). There were no set minimum or maximum numbers of sessions.

2.2. Eligibility

Inclusion criteria for enrollment were as follows: 1) ECT clinically indicated, 2) Males or females 22–80 years of age, 3) Use of effective method of birth control for women of child-bearing capacity, 4) Patient is medically stable (i.e. no serious acute medical condition, generally assessed within the week before the ECT administration and on the morning of the ECT), 5) Capacity of patient to fully participate in the informed consent process as evaluated by their clinician.

Exclusion criteria included the following: 1) Current unstable or serious medical condition, or any co-morbid medical condition that substantially increases the risks of ECT, 2) History of conditions that may make ECT or anesthesia unsafe, 3) Female patients who are currently pregnant or plan to be pregnant during the study.

Patients were allowed to continue on their medications as clinically appropriate but on a fixed dose during the study.

2.3. Assessments

Participants were diagnosed clinically according to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM IV) criteria. Response and remission was determined clinically. Participants were also evaluated using Montgomery-Åsberg Depression Rating Scale (MADRS) (to measure change in depressive symptoms), Mini–Mental State Examination (for global cognitive function assessment) using standard Arabic translation (Al-Rajeh et al., 1999; Folstein et al., 1975) at baseline and endpoint. The 14-question Time to Reorientation test (TRO, the main cognitive measure) assessed the time to reorientation after ECT by asking 14 questions for person specific information (e.g., name, age), time information (e.g., date) and place information (e.g., location). The items are asked at 3, 5, 10, 15, and 20 min following the end of seizure expression as documented on the EEG recording. The TRO score is the time it takes for the patient to be able to answer 14/14 correctly. This test was modeled after and used by the PRIDE study workgroup (Kellner et al., 2016a). In addition to baseline and endpoint assessments, MADRS and MMSE were also done before each session, and TRO after each session. Patients diagnosed with schizophrenia or schizoaffective were also evaluated with Brief Psychiatric Rating Scale to measure change in psychotic symptoms (BPRS). Clinical Global Impression severity score (CGI-S) was used to assess overall change in clinical severity of symptoms. These scales were administered by an experienced staff psychiatrist (E.S). General side effects were assessed clinically by asking the patient if they have any side effects, or if patients simultaneously reported side effects that may be related to the ECT administration.