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Double-blind randomized controlled study showing symptomatic and cognitive superiority of bifrontal over bitemporal electrode placement during electroconvulsive therapy for schizophrenia

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ABSTRACT

Background: Several studies show that bifrontal electrode placement produces relatively fewer cognitive adverse effects than bitemporal placement during electroconvulsive therapy (ECT) in depression. There are no reports comparing these electrode placements in schizophrenia.
Objectives: This study compared the clinical and cognitive effects of bifrontal and bitemporal electrode placements in schizophrenia patients referred for electroconvulsive therapy (ECT).
Methods: 122 schizophrenia patients who were prescribed ECT were randomized to receive ECT with either bifrontal (BFECT; $n = 62$) or bitemporal (BTECT; $n = 60$) placement. Their concomitant antipsychotic medications and the number of ECT sessions were not controlled. Psychopathology was assessed using the Brief Psychiatric Rating Scale (BPRS), Bush-Francis Catatonia Rating Scale (BFCRS), and the Nurse Observation Scale for Inpatient Evaluation (NOSIE). Cognitive functions were assessed 24-h after the final ECT using a battery of tests. Clinical improvement was compared using chi-square test, repeated measures ANOVA and analysis of covariance (ANCOVA). Cognitive adverse effects were compared using *t*-test.
Results: At the end of 2 weeks (after 6 ECT sessions) 63% and 13.2% of BFECT and BTECT patients respectively had met the response criterion for BPRS (40% reduction in total score; OR = 20.8; 95% CI = 3.61–34.33). BFECT patients showed significantly faster clinical response on BPRS (Time × Group interaction effect: $P = 0.001$), BFCRS ($P < 0.001$) and the NOSIE total assets score ($P = 0.003$). ANCOVA using baseline scores as covariates and treatment-resistance status as between-subject factor showed that BFECT patients had significantly greater improvement in all measures. BFECT patients had significantly higher PGI-memory-scale total score than BTECT patients ($t = 5.16$; $P < 0.001$). They also showed superior performance in other cognitive measures.
Conclusions: BFECT results in superior clinical and cognitive outcomes than BTECT in schizophrenia patients referred for ECT.

Introduction

Electroconvulsive therapy (ECT) is arguably the first among the effective biological methods of treatment for schizophrenia. A recent systematic review, which included 26 trials, concluded that ECT, in combination with antipsychotics, is useful in the treatment of schizophrenia – this is particularly so when rapid symptomatic improvement is desired and when there is limited symptomatic improvement with antipsychotics alone [1]. With the advent of antipsychotics, however, the use of ECT for schizophrenia has reduced, particularly in the high-income countries. Professional guidelines restrict the use of ECT in schizophrenia to certain situations – presence of catatonia, suicidal risk and treatment refractoriness find a place in the APA and RCP guidelines [2,3]. However, schizophrenia forms the leading indication among those who receive ECT in many parts of the world, including India [4], Japan [5], Thailand [6], Turkey [7] and Hungary [8]. This situation is true of many teaching institutes of Asia [9]. Expectation that ECT expedites treatment response, thus reducing the duration of inpatient stay, is one of the common reasons why schizophrenia patients receive ECT

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in these countries [10]. Evidently, the speed of response is a prime concern when schizophrenia patients receive ECT.

Cognitive adverse effect is arguably the single most important concern regarding ECT. In depression, most studies [11–15], with a notable exception of a recent study [16], have shown that bifrontal ECT (BFECT) has superiority over the more conventional bitemporal ECT (BTECT) in terms of cognitive adverse effects, while not compromising on the antidepressant effect. In the background of poor research on unilateral ECT (ULECT) in schizophrenia, bilateral ECT (BLECT) remains the most frequent method of treating schizophrenia [4,9].

In this study we compared (1) the speed of therapeutic response to and (2) cognitive adverse effects of BFECT and BTECT using a randomized, double-blind trial in schizophrenia patients referred for ECT. The most important cognitive adverse effect associated with ECT is that of impairment of memory. BFECT is expected to cause lesser impairment of memory, by sparing intense stimulation of the temporal lobes unlike BTECT [17]. In order to examine if the frontal placement of electrodes could cause greater impairment in frontal lobe functions, we included cognitive tests involving the frontal lobe functions, in addition to tests of memory. Consistent with reports in depression [13] and mania [18], we hypothesized that BFECT would result in greater and faster clinical response. We also hypothesized that patients receiving BFECT would have lesser impairment in memory functions and greater impairment in frontal lobe functions than those receiving BTECT.

Methods

Sample

Inpatients of either sex, aged between 18 and 60 yrs, with diagnoses of schizophrenia/schizoaffective disorder, who were prescribed ECT at the National Institute of Mental Health & Neurosciences (NIMHANS), Bangalore, India, were enrolled in this study. Six adult psychiatry units in the Institute, each consisting of a team of junior and senior registrars and consultant psychiatrists, referred patients for ECT. The patients were recruited through two periods: 1st June 2007 to 30th July 2008 and 1st September 2009 to 30th November 2009. The diagnosis of schizophrenia or schizoaffective disorder was made according to the ICD-10 criteria [19] by two qualified psychiatrists, following independent clinical interviews. Mini International Neuropsychiatric Interview (MINI) [20] was used to confirm the diagnosis. Patients were excluded if they had mental retardation, substance use disorder (except nicotine) or major neurological disorder. Those with history of receiving ECT in past two months and those on non-benzodiazepine anticonvulsants were also excluded. As per the routine practice in the Institute, family members stayed with the patients throughout their inpatient period in most [$n = 120$ (98.3%)] cases.

Randomization, allocation concealment and blinding

Patients were randomized, using a computer-generated random number table, to receive either bifrontal or bitemporal ECT (see below under ECT procedure). The patients, their family members and the raters (VHP, BM and PN) were blind to the randomization status throughout the study. The raters were not present in the ECT suite during ECT procedure to ensure blinding; they had no access to ECT records. The investigator (JT) who generated the random sequence was not involved in the recruitment of the patients. The random sequence was kept concealed and the allotment status was revealed to the ECT psychiatrists only after the informed consent was signed, at the first ECT session.

ECT

In all cases, ECT was prescribed by the treating clinical units. No patient was prescribed ECT solely for the purpose of this study; the indications for which ECT was prescribed are described below. Antipsychotic and other medications prescribed by the clinical team were noted, but were not controlled. The standard practice in the Institute is to evaluate all ECT patients with detailed history, mental status and neurological examination, complete blood picture, metabolic work-up, and electrocardiogram. Pre-anesthetic evaluation was obtained for all patients before starting ECT.

ECTs were administered thrice weekly using the NIVIQURE machine (Technonivilac, Bangalore, India) with EEG monitoring. Brief-pulse square-wave stimulation with constant current at 800 mA, 125 bidirectional pulses per second with pulse width of 1.5 ms was used; duration of train was altered to adjust the stimulus dose. All ECTs were administered under anesthetic modification (Thiopentone 2–4 mg/kg & succinylcholine 0.5–1 mg/kg). For BTECT, electrodes were placed on the perpendicular line 3 cm above the midpoint of the line joining the outer canthus of each eye with the ipsilateral external auditory meatus. In BFECT, electrodes were placed bilaterally 5 cm above the outer angle of orbit [18].

During first ECT session, threshold was determined by titration method [21]. From the second session onwards, patients received ECTs of stimuli at 1.5 times their threshold. Seizure duration – both EEG and motor (using the cuff-method), heart rate and blood pressure were monitored. The numbers of abortive and missed seizure as well as details of medication given in the management of prolonged seizure and post-ECT delirium were noted.

Assessment tools

A proforma was designed to collect the details of sociodemographic and clinical variables including type of schizophrenia, duration of total illness in months, duration of current episode in months, duration of anti-psychotic treatment for this episode, dose of antipsychotics in chlorpromazine (CPZ) equivalents in mg/day [22]. Medical and psychiatric co-morbidities along with family history were also recorded. Detailed treatment history was recorded to assess the level of treatment resistance. As the patients were evaluated using research tools after they were referred for ECT, we could not use a prospectively operationalized definition of treatment resistance. History of failure to show clinically significant response to adequate trials at least two anti-psychotic medications was defined as treatment resistance. Twenty (32%) and 17 (28%) patients had history of treatment resistance respectively in BFECT and BTECT groups (Table 1).

1. *Clinical assessment*: The following assessment tools were used before starting ECT (baseline) and the day after every 2nd ECT. The patients receiving odd number of ECTs were assessed 24-h after their last ECT. The ratings on all these scales were based on direct interview by the raters and on the information provided by the ward staff, family members and the resident doctors.
   a. *Brief Psychiatric Rating Scale* (BPRS) [23]: This was used to measure psychopathology. Two raters (VHP and SB) independently scored the BPRS in 30 patients for establishing the inter-rater reliability. Intra-class correlation coefficient for their scores was 0.955 ($P < 0.001$).
   b. *Bush Francis Catatonia Rating Scale* (BFCRS) [24]: This was used only in those with catatonic symptoms.
   c. *Nurses Observation Scale for Inpatient Evaluation* (NOSIE) [25]: Two trained psychiatric nurses (BM & PN) administered this to assess the overall behavior of the patients. The NOSIE assesses inpatient behaviour across 14 'positive'