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Effectiveness and clinical predictors of response to combined ECT and antipsychotic therapy in patients with treatment-resistant schizophrenia and dominant negative symptoms

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ABSTRACT

The effectiveness and predictors of response to electroconvulsive therapy (ECT) combined with antipsychotics (AP) in treatment-resistant schizophrenia patients with the dominance of negative symptoms (TRS-NS) have not been studied systematically so far. 29 patients aged 21–55 years diagnosed with TRS-NS underwent ECT combined with antipsychotics (ECT+AP). Prior to the ECT, the symptom profile and severity were evaluated using Positive and Negative Syndrome Scale (PANSS). Demographic and medical data was collected; ECT parameters and pharmacotherapy results were evaluated. After the combined ECT+AP therapy a significant decrease in symptom severity was found. A response to treatment was achieved by 60% of patients. The greatest reductions were obtained in general and positive PANSS subscale (median change: 11 and 7 pts.) and the smallest, but still significant, ones in negative symptoms subscale (median: 3.5 pts.). Patients who responded to ECT+AP demonstrated a significantly shorter duration of the current episode in comparison with patients who did not experience at least a 25% reduction in symptom severity (median: 4 vs. 8 months). A combination of ECT and antipsychotic therapy can provide a useful treatment option for patients with TRS-NS. The only significant predictor of response to treatment was a shorter duration of the current episode.

1. Introduction

Resistance to pharmacotherapy in schizophrenia patients is a common and important clinical problem. Definitions of treatment resistance can differ significantly: in the kind of ineffective antipsychotics (APs), duration of treatment, psychopathological symptoms and the psycho-social functioning of the patient (Brenner et al., 1990; Bondolfi et al., 1998; Peuskens, 1999). According to NICE (National Institute for Health and Clinical Excellence) treatment-resistant schizophrenia has been defined as failure of improvement of the target symptoms despite an adequate trial of medication for 6–8 weeks with adequate dosing of at least two groups of APs (NICE, 2003). Data on prevalence of treatment-resistant schizophrenia varies and depends on the accepted criteria. Considering mild to severe positive and/or negative symptoms, approximately 15–30% patients with schizophrenia qualify for treatment-resistant schizophrenia after they have undergone two or more therapies of adequate dosing with APs for at least 6 weeks (Meltzer, 1997). Electroconvulsive therapy (ECT) may be used in patients resistant to clozapine or for whom clozapine is contraindicated and also after obtaining a therapeutic effect, maintenance ECT should be considered. The American Psychiatric Association recommends ECT as the treatment of choice in ineffective pharmacotherapy or good response to ECT in the previous episodes of the disease, or second choice treatment in treatment-resistance eg., in schizophrenia (Weiner, 2001). Several studies and meta-analyses showed efficacy and safety of ECT+AP therapy in patients with TRS (Painuly and Chakrabarti, 2006). Mainly first generation antipsychotics or clozapine were used in the conducted studies (Chanpattana et al., 1999b; Biedermann et al., 2011). Only a limited number of papers can be found on the combined use of ECT and second generation antipsychotics (SGAs) (Tang and Ungvari, 2002; Masdrakis et al., 2008b; Ravanic et al., 2009; Masdrakis et al., 2010; Takacs et al., 2013). Patients who present mainly with negative symptoms of schizophrenia constitute a difficult group of patients to treat, especially in patients with treatment-resistant disease. Positive symptoms of schizophrenia respond better to ECT, thus the technique of therapy is indicated mainly in patients with the dominance of positive symptoms (Chanpattana et al., 1999a; Chanpattana and Sackeim, 2010). Little

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is known about the efficacy of the combined ECT+AP therapy in patients with TRS-ND group of patients. Ravanic et al. (2009) described the efficacy of electroconvulsive therapy combined with different antipsychotic drugs in previously resistant schizophrenia. The study population was composed of 70 TRS patients, 33 of whom had dominant negative symptoms. No separate analyses were performed in TRS-NS group. The effectiveness of the combined ECT+AP therapy in patients with TRS-NS was not evaluated systematically so far. Predictors of response to combined therapy were also not identified in that special population of patients. To the best of our knowledge it is the first report describing the effectiveness and response predictors to ECT+AP therapy in TRS patients with the dominance of negative symptoms.

1.1. Aim of the study

The aim of the study was to determine: (a) the effectiveness, and (b) predictors of response to combination ECT+AP therapy in patients with treatment-resistant schizophrenia and the dominance of negative symptoms (TRS-NS). Potential predictors were selected according to the results of previous studies (Chanpattana and Chakrabhand, 2001; Chanpattana and Sackeim, 2010) performed in patients with TRS and consisted of initial symptom profile (severity of positive or negative symptoms and comorbid depressive symptoms); demographic variables (age and gender); duration of the disease and duration of the current episode and a form of pharmacotherapy used.

2. Methods

2.1. Setting and patients

Twenty-nine adult patients (15 males and 14 females), aged 21–55 years (mean age=32.8 years) diagnosed with schizophrenia according to ICD-10, treated with ECT in the Department of Psychiatry, Central Teaching Hospital, Medical University of Lodz and psychiatric wards in Dr. J. Babiński's Hospital in Lodz were enrolled in the study. Although 31 patients were enrolled, only 29 patients completed the study. Two patients did not start ECT because they withdrew consent to participate. Twenty nine patients accomplished the study and were included in the analyses. The study inclusion criteria comprised patients age 18–60 years, diagnosed with schizophrenia according to ICD-10 criteria, with drug resistance defined according to criteria described below. Only patients diagnosed with treatment-resistant schizophrenia with the dominance of negative symptoms (TRS-NS) over positive ones scored by means of Positive and Negative Syndrome Scale (PANSS) were enrolled in the study. The study exclusion criteria were as follows: serious medical disorders contraindicated for ECT, inability to sign informed consent because of incapacity due to severe mental illness, significant psychomotor agitation or slowness test completion, current use of alcohol or psychoactive substances, dominance of positive symptoms over negative. The age of the disease onset in the population of patients enrolled in the study was between 16 and 33 years of age (mean age: 21.6 years).

Mean disease duration at the time of the study was 11.2 years. Family history of schizophrenia in first degree relatives was positive in 18 and negative in 11 patients. All participants received long-term treatment and were hospitalized several times – mean number of hospitalizations was 5.8, mean duration of the current exacerbation was 7.2 months.

The diagnosis of treatment-resistance was based on medical records, medical history and clinical examination. Patients were considered treatment resistant according to American Psychiatric Association criteria (American Psychiatric Association., 2004). Treatment resistance was defined as little or no symptomatic response to multiple (at least two) courses of antipsychotics of an adequate duration (at least 6 weeks) and dose (therapeutic range). The research study protocol was approved by Biomedical Ethics Committee of Medical University of Lodz. Informed consent for the study was obtained from all subjects before undergoing procedures.

2.2. Electroconvulsive therapy technique

Each patient was given ECT 3 times a week in an acute psychiatric unit. A brief-pulse machine generating bipolar, square waves (The Thymatron® System IV, Somatics, LLC, Lake Bluff, IL, United States) was used. Propofol (1.25–2.0 mg/kg) was used as an anesthetic agent and succinylcholine (0.5–1 mg/kg) as a muscle relaxant. Atropine (0,5–1,0 mg) and clemastine (2 mg) were also routinely administered in all participants. Etomidate (0.15–0.3 mg/kg) anesthesia was used instead of propofol in patients experiencing short episodes of seizures in spite of the high energy charge used. Bitemporal bilateral electrode placement was used exclusively. Seizure thresholds were estimated at the first and the last treatment sessions, using the empirical titration technique. An adequate seizure was defined as at least 30 s of tonic–clonic motor activity with electroencephalographic (EEG) evidence of a seizure. Electrical dose was maintained at the threshold level unless short seizures occurred; then, charge was increased by 50%. The total number of ECT sessions for each patient was determined by the authors' consensus opinion based on clinical improvement and adverse side effects. A complete course of 16–20 ECT sessions was intended unless adverse effects and/or patient's refusal shortened the course. The mean number of ECT sessions was 13.1 (12–20 sessions).

2.3. Concurrent antipsychotic medication

All patients undergoing ECT were treated with APs. Monotherapy was used in 18 patients and 10 patients received combination of two APs. SGAs were administered to 78% of patients on monotherapy: olanzapine, clozapine, amisulpride, quetiapine and ziprasidone were used most frequently. Patients on polypharmacotherapy were given a combination of SGAs with adjuvant FGAs or the second SGA. The FGAs most frequently used in polypharmacotherapy were perphenazine and haloperidol. A combination of two FGAs was not given. Most commonly clozapine, olanzapine and amisulpride were used. Mean number of APs therapies in the current episode was 3.3. AP dosage was not given in the evening before and in the morning of the day ECT was administered. New therapies with APs were not begun in the course of ECT.

2.4. Psychiatric assessment and measures

The patients were examined twice: before starting ECT (t1) and within 3 days after finishing ECT sessions (t2). Rating scales to evaluate changes in the patients' mental status included the Positive and Negative Syndrome Scale – PANSS, the Calgary Depression Scale for Schizophrenia – CDSS, Clinical Global Impression-Severity – CGI-S and Clinical Global Impression-Improvement – CGI-I. One author (E.K-K. – specialist psychiatrist), who did not have direct clinical responsibility for the patients, rated all the clinical scales. The rater had undergone extensive training in the use of the mentioned scales prior to study participation and received high inter-rater reliability scores. A self-made questionnaire was used to collect demographic and medical data. Table 1 presents data concerning the characteristics of investigated population and mental status before starting ECT.

2.5. Statistical analysis

Descriptive statistics were used to characterize the demographic and clinical data of the study sample. Statistical analyses included descriptive and inference methods. Since distributions assessed with Shapiro–Wilk test revealed significant discrepancies from the normal range, nonparametric techniques were used. Changes in clinical scales scores between baseline evaluation before ECT initiation (t1) and the assessment following the course of ECT (t2) were compared using Wilcoxon signed-rank test. In order to assess differences between groups, the absolute change scores between baseline and t2 were calculated, and the results were compared using Mann–Whitney test. Relationships between qualitative variables were assessed using Chi-square test. When the expected number of cases in the frequency table cell was smaller than five, Fisher's exact test was used. A decrease in the PANSS total score by at least 25% was taken as response to treatment. A percentage change of scores was calculated according to the Leucht et al. algorithm (Leucht et al., 2007) assuming that a patient with no psychopathological symptoms scores 1 in all PANSS items. The patients were then categorized according to decrease in clinical symptom severity obtained in the course of the therapy $\geq 25\%$ or $< 25\%$ of the initial symptom score. Next the statistical significance of differences in distribution of quantitative variables according to treatment response was evaluated. The number of subjects enrolled in the study did not allow multi-dimensional analysis to be performed. All calculations were done using Statistical Package for Social Sciences (SPSS for Windows, version 12).

3. Results

3.1. Changes in symptom severity after ECT+AP therapy in treatment-resistant schizophrenia patients

A significant decrease in symptom severity in all PANSS subscales was observed. The mean decrease in PANSS total score was 32%; the greatest improvement was found in the positive subscale, a 37.5% decrease in symptom severity, while the smallest was in the negative subscale: 23.8%. In total, 60% of the group responded

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