Maintenance ECT in Treatment-Resistant Schizophrenia†

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Abstract

Although electroconvulsive therapy (ECT) has been used to treat schizophrenia since its inception in 1938, its efficacy as long-term treatment is still controversial. A 2-Phase, prospective study has been conducted in 21 patients with schizophrenia. The duration of study was 1 year. Bilateral ECT combined with flupenthixol (18-24 mg/day) was used throughout. Brief Psychiatric Rating Scale (BPRS), Global Assessment of Functioning (GAF), and Mini-Mental-State Exam (MMSE) were used to measure the outcome. No patients suffered relapses. There were marked reductions in BPRS scores (73 per cent and 70 per cent), and increases in GAF scores (68 per cent and 91 per cent), at the end of Phases I and II, respectively. This study suggests a long-term efficacy of ECT combined with neuroleptic therapy in patients with schizophrenia.

Key word : Electroconvulsive Therapy (ECT), Maintenance ECT, Treatment-Resistant Schizophrenia, Prospective Study

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Electroconvulsive therapy (ECT) has been used to treat schizophrenia since its inception in 1938[1]. Whereas the short-term efficacy of combined ECT and neuroleptic therapy in schizophrenic patients has been recently established[2,3], the benefit of long-term treatment is still a highly debatable issue.

The use of maintenance ECT (M-ECT) as a treatment for schizophrenia was first reported by Moore[4] and Kalinowsky[5] in 1943. At the present time, there have been 13 reports on M-ECT in schizophrenia[6-9], with only 8 studies done exclusively concerning patients with schizophrenia[2,3,8-13]. Unfortunately, there is only one study[3] using

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standardized assessment methods with methodologically acceptable research design, but the duration of the study was only six months.

By using modern ECT technique, this study was conducted prospectively in 21 patients with schizophrenia to add more data on the therapeutic efficacy of M-ECT.

METHOD

Twenty-one patients with acute psychotic exacerbations, and with DSM-IV criteria for schizophrenia[14], were referred for ECT because of failure to respond to neuroleptic treatment. All met a criterion for treatment-resistant schizophrenia (TRS) used in our prior work[2,3], and were part of our other studies[15,16]. Other inclusion criteria were a minimum pretreatment score of 37 on the Brief Psychiatric Rating Scale [BPRS, [17]], age 16-50 years, and written consent obtained from patients and/or their guardians. Patients were excluded if they had organic mental syndrome, neurological illness, alcohol or other substance abuse, serious medical illness, or hypersensitivity to medications used in modified ECT (thiopental and succinylcholine). All patients had normal results of complete blood count, serum electrolytes, and electrocardiogram.

The study was divided into two phases, described in the following sections.

Phase I (Acute Treatment Study)

Neuroleptic medications prescribed prior to the study were discontinued, without a washout period. Flupenthixol was started before the first ECT session, and was continued throughout the study. The dosage schedule of flupenthixol was fixed: 12 mg/day during the first week and increased to 24 mg/day depending on tolerability. Benzhexol (4-15 mg/day) was used to control extrapyramidal symptoms, with dosage titrated on a clinical basis. No other medications were prescribed.

ECT was administered three times per week. The ECT devices were a MECTA SR1 and Thymatron DGx. Anesthesia was with intravenous thiopental 2-4 mg/kg and succinylcholine 0.5-1 mg/kg. Ketamine (1 mg/kg) was used as a replacement in patients in whom seizure duration was shorter than 30 seconds at the maximal charge settings of the ECT device. The traditional bilateral electrode placement was used throughout. One adequate seizure was elicited in each treatment, which was defined as a tonic-clonic convulsion occurring bilaterally for $\geq$ 30s plus electroencephalogram (EEG) evidence of a cerebral seizure. The electrical dosing schedule suggested by Srinakharinwirot University (SWU) for the MECTA SR1 and Thymatron was used[18]. Patients' seizure threshold was identified in the first treatment. In a case of missed or short seizures, charge was increased by 50 per cent (one step in the titration schedule) at each subsequent treatment.

The criterion for clinical response corresponded to a BPRS score of 25 or less, as described in prior studies[8,9]. The patients who manifested this level of clinical improvement, went on to a 3-week stabilization period[2,3,9,19]. The ECT responders were patients who could pass this 3-week period, during which, the BPRS scores assessed before each treatment were always $\leq$ 25.

Measures used to assess the study outcome were: 1) BPRS assessed before each treatment during the acute and stabilization periods, and the end of Phase I study (1 week after the last treatment); 2) Global Assessment of Functioning (GAF) assessed before acute treatment, and at the end of the study; and, 3) the Mini-Mental-State Exam (MMSE) assessed at the same time as the BPRS. Three psychiatric nurses served as raters. Each patient was rated by the same nurse. Inter-rater reliability was assessed, the details of which are described elsewhere[3,20]. The correlations of BPRS scores between each rater and the psychiatrist indicated strong reliability (0.93, 0.95, and 0.97).

Phase II (Maintenance Treatment Study)

All patients met our selection criteria (a 3-week stabilization period) for the maintenance treatment study. The duration of Phase II study was one year. M-ECT was started one week after the last treatment of the stabilization period, on an outpatient basis. Using a fixed schedule during the first 6 months: beginning with weekly treatment for 1 month and biweekly for 5 months. Then, M-ECT schedule was based on the following considerations: 1) BPRS scores, 2) history of responsiveness to prior ECT, and, 3) requests from patients and guardians. Fourteen patients received biweekly, one triweekly, and 6 monthly treatments. Flexibility was allowed to schedule each treatment within a 3-day window. No additional treatments were given outside this schedule. The dosages of flupenthixol and benzhexol were kept fixed as in the Phase I study,

and were continued throughout Phase II. The ECT treatment procedures were similar to Phase I.

Outcome measurements were: 1) BPRS assessed just before each treatment, and 1 week after the end of Phase II treatment; 2) GAF assessed before the first Phase II treatment, at the first, third, sixth, ninth months, and 1 week after the end of Phase II treatment; and 3) MMSE assessed at the same time as BPRS. Relapse was defined as a BPRS score of $\geq$ 37 that persisted for two consecutive ratings, 3 days apart.

RESULTS

Table 1 presents the demographics and clinical characteristics of the sample patients. Twenty-one TRS patients underwent acute treatment, and maintained remitter status through the stabilization period. There were marked clinical improvements as evidenced by a reduction in BPRS scores (73.2 $\pm$ 14.1%, t = 15.4, df = 1,20, p < 0.0001), increased GAF scores (68.2 $\pm$ 30.9%, t = 12.1, df = 1,20, p < 0.0001), and increased MMSE scores (9.7 $\pm$ 12.0%, t = 4.0, df = 1,20, p = 0.001) at the end of Phase I study.

Table 1. Patient characteristics (n = 21).

Variable	Mean $\pm$ SD (range)
Age (yr)	32.2 $\pm$ 7.2 (22-45)
Sex	16 female, 5 male
Subtype	18 paranoid, 2 disorganized, 1 catatonia
Onset of illness (yr)	21.5 $\pm$ 5.1 (13-32)
Duration of illness (yr)	10.8 $\pm$ 6.2 (3-25)
Episode duration (yr)	1.1 $\pm$ 1.3 (1mo-5yr)
Prior psychiatric admission	5.1 $\pm$ 4.1 (1-15)
Prior failure of adequate neuroleptic trials	3.8 $\pm$ 0.9 (3-6)
CPZ equivalence (mg)	1157.4 $\pm$ 312.5 (800-2080)
Duration of each neuroleptic trial (mo)	14.4 $\pm$ 13.8 (2.4-50)
Prior failure of flupenthixol treatment	12
History of prior ECT responsiveness	14
Family history of schizophrenia	2
BPRS at Phase I entry	50.5 $\pm$ 9.1 (37-67)
GAF at Phase I entry	32.2 $\pm$ 5.1 (25-45)
MMSE at Phase I entry	26.9 $\pm$ 3.2 (20-30)
Number of index ECT treatment	11.4 $\pm$ 5.0 (7-23)
Stimulus charge (mC)	202.1 $\pm$ 106.8 (83-417)
Seizure duration – motor (s)	40.1 $\pm$ 9.2 (24-57)
– EEG (s)	48.5 $\pm$ 10.0 (31-65)
Thiopental (mg)	143.3 $\pm$ 31.1 (100-250)
Succinylcholine (mg)	23.7 $\pm$ 6.0 (12.5-37.5)

Table 2. Changes in BPRS, GAF, and MMSE scores of Phases I and II.

	BPRS	GAF	MMSE
At Phase I entry	50.5 $\pm$ 9.1 (37-67)	32.2 $\pm$ 5.1 (25-45)	26.9 $\pm$ 3.2 (20-30)
End of Phase I[a]	13.1 $\pm$ 6.6 (3-25)	53.4 $\pm$ 8.4 (37-65)	29.2 $\pm$ 1.6 (24-30)
Phase II -1st month	15.0 $\pm$ 8.4 (2-32)	54.0 $\pm$ 9.3 (38-68)	28.8 $\pm$ 1.7 (24-30)
-3rd month	15.0 $\pm$ 9.4 (3-31)	53.4 $\pm$ 11.0 (38-72)	29.4 $\pm$ 1.2 (26-30)
-6th month	14.7 $\pm$ 9.4 (3-33)	56.6 $\pm$ 12.9 (36-79)	29.6 $\pm$ 0.7 (28-30)
-9th month	16.5 $\pm$ 9.6 (2-32)	55.1 $\pm$ 11.2 (38-76)	29.5 $\pm$ 0.9 (28-30)
End of Phase II[b,c]	14.2 $\pm$ 7.8 (2-29)	60.3 $\pm$ 11.0 (38-78)	29.8 $\pm$ 0.5 (28-30)

[a] Changes in Phase I: BPRS- t = 15.4, df = 1,20, p < 0.0001; GAF- t = 12.1, df = 1,20, p < 0.0001; MMSE- t = 4.0, df = 1,20, p = 0.001
[b] Changes in Phase II: BPRS- t = 0.6, df = 1,20, p = 0.59; GAF-t = 2.4, df = 1,20, p = 0.024; MMSE- t = 1.9, df = 1,20, p = 0.07
[c] Overall changes: BPRS- t = 11.8, df = 1,20, p < 0.0001; GAF- t = 11.2, df = 1,20, p < 0.0001; MMSE- t = 4.2, df = 1,20, p < 0.0001

During Phase II study, patients still gained benefits from M-ECT as manifested by 15.3 ± 25.8% increases in GAF scores ($t = 2.4$, $df = 1,20$, $p = 0.024$). For both Phases I and II, there was 69.9 per cent reduction in BPRS scores, and 90.8 per cent and 12.3 per cent increases in GAF and MMSE scores, respectively. No patients suffered relapses at the end of Phase II. Table 2 shows changes in BPRS, GAF, and MMSE scores at each assessment.

DISCUSSION

This study supports the therapeutic benefits of M-ECT in 21 patients with TRS over a 1-year period. All patients manifested satisfactory improvement. The scientific merit of our study is limited by the small number of sample patients, and lacking a group for comparison. Nevertheless, the results coincide with our prior studies[2,3,9,16,17].

Although between 10-15 per cent of patients with schizophrenia are treatment resistant at the onset of the illness[21], 30-60 per cent of the remaining patients eventually become treatment resistant or partially responsive to treatment[22]. Therefore, a substantial number of patients develop either the capacity to be refractory to treatment or a more severe clinical course that no longer responds to treatment. Clozapine, the first of the atypical neuroleptics, is effective in 30-50 per cent of patients with TRS[23-25]. At the present time, there is no confirmatory evidence that any of the newer atypical neuroleptics (i.e., risperidone, olanzapine, sertindole) are as effective as clozapine. Thus, seeking a more effective or alternative treatment for TRS remains a clinical challenge, in spite of its controversial definition[26].

The antipsychotic activity of neuroleptics appears to be augmented by ECT. The studies of Childers & Therrien[27] and Smith et al[28] were the forerunners of many other works in schizophrenic patients. Recently, two studies have demonstrated the efficacy of combined ECT and neuroleptic treatment in patients with TRS, one of which is a short-term[2] and the other long-term[3].

In our subject sample, there were 6 patients who previously failed to respond to adequate treatment with atypical neuroleptics. Four patients did not respond or poorly responded to risperidone 6-8 mg/day over 3-6 months, one was poorly responsive to clozapine 600 mg/day during a continuous period of treatment (9 months), and the last patient failed to respond to both risperidone 8 mg/day (3 months) and clozapine 500 mg/day (2 months).

In summary, ECT combined with neuroleptics therapy may be effective as both acute and maintenance treatments in patients with TRS. The scientific merit of this study is limited by a lack of group for comparison and the small numbers.

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การรักษาด้วยไฟฟ้าชนิดต่อเนื่องในผู้ป่วยจิตเภทเรื้อรังที่ดื้อต่อการรักษา†

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แม้ว่ามีการเริ่มใช้การรักษาด้วยไฟฟ้าในผู้ป่วยจิตเภทมาตั้งแต่ปีพ.ศ. 2481 แต่จนถึงปัจจุบันก็ยังไม่ทราบถึงประสิทธิภาพระยะยาว การศึกษานี้ทำในผู้ป่วยจิตเภทเรื้อรังที่ดื้อต่อการรักษาจำนวน 21 ราย เป็นชนิด prospective, open-trial มี 2 phases ได้แก่ acute และ continuation treatment studies ระยะเวลาศึกษานาน 1 ปี ให้ยารักษาโรคจิตร่วมกับการรักษาด้วยไฟฟ้าชนิด bilateral มีการประเมินผลผู้ป่วยด้วย Brief Psychiatric Rating Scale (BPRS), Global Assessment of Functioning (GAF), และ Mini-Mental State Exam (MMSE)

ไม่มีผู้ป่วยใดมีการกำเริบของโรค พบว่ามีการลดลงของคะแนน BPRS ร้อยละ 73 และ 70 และมีการเพิ่มขึ้นของคะแนน GAF ร้อยละ 68 และ 91 ที่สิ้นสุดการศึกษาในแต่ละ phase ตามลำดับ

การศึกษานี้สนับสนุนประสิทธิภาพระยะยาวของการรักษาด้วยไฟฟ้าร่วมกับการใช้ยารักษาโรคจิต ในผู้ป่วยจิตเภทเรื้อรังที่ดื้อต่อการรักษา

คำสำคัญ : การรักษาด้วยไฟฟ้าชนิดต่อเนื่อง, โรคจิตเภทเรื้อรังที่ดื้อต่อการรักษา, ประสิทธิภาพ, ระยะยาว

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