The Use of the Stabilization Period in ECT Research in Schizophrenia : I. A Pilot Study†

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Abstract

Electroconvulsive therapy (ECT) has been used to control schizophrenic patients since 1938. At the present time, the role of ECT treatment in schizophrenia is still controversial. This is because of the paucity of research of both acute and long term ECT uses, which has also been characterized by serious methodological flaws. The main problems of these difficulties are : 1) lacking standard of ECT techniques, 2) using heterogeneous groups of patients, and, 3) no proper outcome measurements. The author hypothesized *the 3-week-stabilization- period* in order to use as : 1) a response criterion to delineate the ECT responders from non-responders, 2) a screening method to obtain a homogeneous group of patients for continuation treatment study in schizophrenia, and 3) a method to terminate acute ECT treatment. This pilot study was done prospectively on 35 schizophrenic patients suffering psychotic exacerbations. Twenty three patients passed the stabilization period and there were a clear distinction between responders and non-responders. This study could identify a homogeneous group of patients, which might be suitable for continuation treatment study. Critical questions regarding the ECT methodological issues are extensively discussed.

Key word : ECT, Schizophrenia, Therapeutic Efficacy, Prospective Study, Stabilization Period

Schizophrenia affects just under 1 per cent of the world's population. The psychosis usually manifests during late adolescence and early adulthood. Therefore, it causes significant and long-lasting impairments, makes heavy demands on hospital care, and requires ongoing clinical care, rehabilitation, and support services. The financial cost of illness in the United States is so high that it was estimated to be about one-third of the cost for all mental illnesses for 1988(1).

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Using intramuscular injection of camphor, Meduna was the first to deliberately induce seizures with the aim of treating schizophrenia in 1934[2]. Cerletti and Bini introduced the use of electricity as a method of seizure induction, again with the intent of treating schizophrenia in 1938[3]. Since then, electroconvulsive therapy (ECT) has gained popularity in treating schizophrenic patients and its use has been extended to a number of disorders[4]. The introduction of neuroleptic drugs in the late 1950s led to a sharp drop in ECT utilization. During the 1970s, when limitations on their efficacy in treating schizophrenia and some adverse effects from prolonged use were recognized, the interest in ECT as a treatment for therapy resistant patients returned[5,6].

Unfortunately, the role of ECT treatment in schizophrenia is still controversial at the present time. There have been no methodologically accepted studies documenting the effectiveness of ECT treatment in such patients. The major difficulties in research methodology can be summarized as : 1) there have been no prospective, double-blind, random assignment studies contrasting the efficacy of ECT with pharmacological treatment of schizophrenia; 2) a lack of standard of ECT techniques; 3) using heterogeneous groups of patients; and, 4) lacking proper outcome measurements[5-10].

The author hypothesized *the 3-week-stabilization-period*, used during acute ECT treatment, in order to use as: 1) a response criterion to delineate the ECT responders from non responders, 2) a screening method to obtain a homogeneous group of patients for continuation treatment study, and 3) a method to justify the optimal number of ECT treatments, which is always an important concern when considering the termination of ECT courses[11]. Therefore, a more homogeneous group of patients could be obtained for the continuation treatment study, which might be of great benefit in the treatment comparison studies in patients with schizophrenia.

METHOD

Thirty five schizophrenic patients who suffered acute psychotic exacerbations were referred to the ECT unit of Vajira Hospital from July 1994 to January 1996. All met DSM-III-R criteria[12] of schizophrenia as assessed by the ward staff. They had received no ECT treatment during the month prior to this study. All underwent acute treatment with ECT alone. All neuroleptics prescribed before entering the study were immediately discontinued, and there was no wash-out period. None of these patients had serious medical conditions by history, physical examination or appropriate laboratory tests e.g. CBC, blood chemistry, electrolytes, chest X-ray and electrocardiographs. Consent was obtained from the patients and/or their guardians. Diazepam was the only medication prescribed to control agitation on a prn basis. Clinical responses were evaluated by ward staff who were not part of this study. ECT treatments were given three times per week. The ECT device was MECTA-SR1. Thiopental (2-4 mg/kg) was used as an anesthetic agent and succinyl choline 0.5-1 mg/kg as a muscle relaxant. Bilateral electrode placement was used throughout this study. In each treatment only one adequate seizure was required. An adequate seizure is defined, in this study, as a tonic-clonic convulsion occurring bilaterally for at least 30 seconds plus an electroencephalogram (EEG) showing evidence of cerebral seizures. Measurements used for the study outcome were : Global Assessment of Functioning (GAF), Brief Psychiatric Rating Scale (BPRS),[13] and, Thai Mental State Exam (TMSE)[14]. A single psychiatric nurse was used as a rater, and was not otherwise involved in any part of the treatment.

At the first signs of clinical improvement, reported by the ward staff, the patients' BPRS scores were immediately assessed. Then, these patients went on to pass a *3-week-stabilization-period*, the hypothesized treatment schedule, in which these improvements had to be sustained (Fig. 1). The stabilization period comprised the following treatment schedule : 3 regular ECT (3 treatments/week) in the first week, then once a week for the second and third weeks, during which the same BPRS scores (or below, but not increased) always had to be achieved. If the BPRS scores rose above their first assessments any time during this period, and the total number of ECT treatments was less than 20, these patients had to go back to receive regular ECT treatments and repeat the above schedule again. The patients whose BPRS scores were still more than their first assessments, and had already received 20 ECT treatments, were considered *ECT nonresponders*. The *ECT responders* were the patients who were able to pass the 3-week-stabilization-period, during which, their BPRS scores were assessed before each treatment and were always either equal to or less than their first assessments. The BPRS

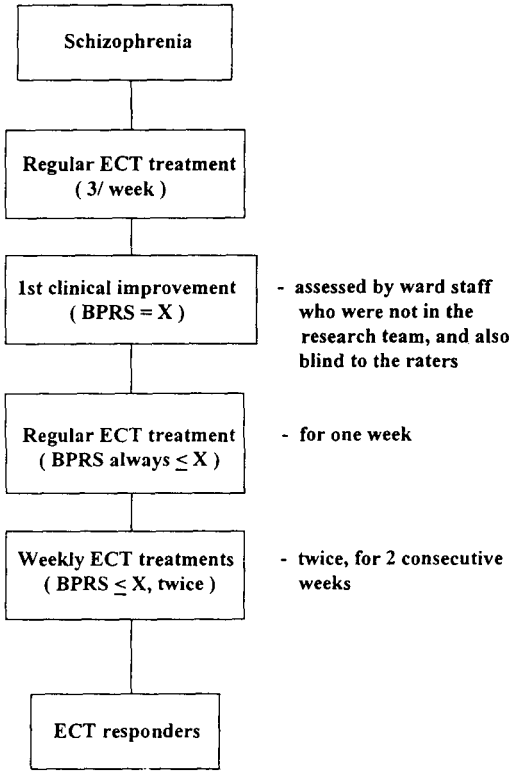

Fig. 1. The 3-week-stabilization-period.

scores of the last treatments were called *baseline BPRS*. All of the responders were assessed for their BPRS scores at one week after their last treatments (end of study).

RESULTS

Thirty five schizophrenic patients underwent acute treatment. Three patients dropped out, leaving 32 patients in the study. All of the drop-outs gave their reasons as fear of ECT. Twenty three patients were able to pass the stabilization period, and they were then identified as ECT responders. Nine patients still had BPRS scores higher than their first assessments, and were considered ECT nonresponders.

Table 1 shows the demographics and clinical data of all 35 patients, which are divided into 3 groups : ECT responders, nonresponders, and drop-outs. There was a tendency to have some differences between the ECT responders and drop-outs and the nonresponders.The nonresponders were older (30.8 ± 4.2 yrs, range: 25-38 yrs), had a longer duration of illness (12.0 ± 4.2 yrs, range: 5-16 yrs), a longer duration of current episode (7.5 ± 4.5 yrs, range: 2.5-14 yrs), more previous psychiatric admissions (6.6 ± 6.1, range: 2-14), received more ECT treatments (20.9 ± 1.8, range: 20-24) compared to the responders and drop-out groups (27 ± 7.5 & 25.7 ± 3.7 yrs, range: 22-41 & 22-30 yrs; 5.6 ±

Table 1. Demographics and clinical data.

Variable	Responders* [N=23, mean±SD, range]	Nonresponders (N = 9)	Drop-outs (N = 3)
Age (yr)	27.0 ± 7.5 (22-41)	30.8 ± 4.2 (25-38)	25.7±3.7 (22-30)
Sex	14F, 9M	5F, 4M	1F, 2M
Subtype**	14P, 6D, 3C	4P, 2D, 3U	2P, 1D
Onset of illness (yr)	22.5 ± 6.9 (15-33)	19.8 ± 4.4 (16-22)	22 ± 1.7 (20-25)
Duration of illness (yr)	5.6 ± 2.9 (1-11)	12.0 ± 4.2 (5-16)	2.1± 2.5 (1-5)
Current episode duration (yr)	0.9 ± 0.9 (0.08-2)	7.5 ± 4.5 (2.5-14)	0.3±0.2 (0.2-0.5)
Prior psychiatric admissions	3.3 ± 3.6 (1-10)	6.6 ± 6.1 (2-14)	2.8 ± 3.6 (1-7)
Prior neuroleptic trials	3.5 ± 1.6 (1-6)	4.0 ± 3.1 (2-6)	2.1 ± 1.8 (1-4)
Number of acute treatments	14.8 ± 6.6 (8-24)	20.9 ± 1.8 (20-24)	-
BPRS - on admission	44.1 ± 8.4 (37-56)	48.8 ± 3.9 (38-56)	50.9±11.1 (42-64)
- end of study	19.6 ± 6.8 (5-33)***	43.3 ± 8.8 (32-60)***	-
- % of reductions	61.3 ± 12.5 (35-85)	13.2 ± 21.5 (50%-30% increase)***	
TMSE - on admission	28.4 ± 2.1 (24-30)	26.2 ± 4.0 (20-30)	28.0±2.1 (25-30)
- end of study	28.1 ± 2.2 (22-30)	24.0 ± 4.8 (16-30)	-
GAF - on admission	30.3 ± 6.1 (22-38)	30.1 ± 4.8 (24-35)	32.5±4.4 (26-36)
- end of study	54.5 ±7.1 (35-65)***	33.4 ± 5.6 (24-38)***	-

* 'Responders' is defined by the criteria used in this study.
** Subtype : P = paranoid, D = disorganized, C = catatonic, U = undifferentiated
*** $p < 0.0001$

2.9 & 2.1 ± 2.5 yrs, range: 1-11 & 1-5 yrs; 0.9 ± 0.9 & 0.3 ± 0.2 yrs, range: 0.08-2 & 0.2-0.5 yrs; 3.3 ± 3.6 & 2.8 ± 3.6, range: 1-10 & 1-7; and 14.8 ± 6.6, range: 8-24, respectively).

The responders had a marked reduction in their BPRS scores (61.3 ± 12.5%, range: 35-85%), compared to the nonresponders (13.2 ± 21.5%, range: 50 per cent decrease to 30 per cent increase). There were no statistically significant differences between the BPRS scores of each treatment schedule during the 3-week-stabilization-period, and between the baseline BPRS scores and the BPRS scores at the end of study (Table 2).

DISCUSSION

In summary, 23 of 32 patients were able to pass the 3-week-stabilization-period, and were ECT responders by the criteria used in this study. The responders had a marked reduction in their BPRS scores and could be delineated clearly from the nonresponders. Furthermore, there were no statistically significant differences of their BPRS scores in each assessment beginning from the first regular ECT treatment (R1) of the stabilization period to the end of study. Therefore, these patients could represent a homogeneous group of patients that is an ideal sample for the continuation treatment study. The number of ECT treatments of the patients was also justified by their abilities to pass the stabilization period or the minimal number of ECT treatments of 20 (in the nonresponders). The assessment of psychotic symptoms by using the BPRS depends largely on the rater(s)'s clinical experience, so that the rating standard must be evaluated in each institution before its use. The cut-off point of the BPRS scores was obtained by using the BPRS scores at the time of first improvement of each patient, which were 23.1 ± 2.7 (range: 18-27). For practical purposes, the author used the BPRS score of 25 either as a cut-off point of the result of acute treatment study or as an important part of the criteria for relapse of the continuation treatment study of our institution. Therefore, the hypothesized *3-week-stabilization-period* was able to complete all of the author's objectives described previously. This is the first ECT study using the stabilization period in English language literature.

There has been no prospective, double-blind, random assignment study contrasting the efficacy of ECT and neuroleptic treatment with neuroleptic treatment alone in schizophrenic patients. The literature is characterized by a host of methodological difficulties. Similarly, there has been a dearth of research on relapse and continuation pharmacotherapy following response to ECT[15]. The central questions regarding ECT methodology issues in schizophrenia research study would seem to be: 1) Who should be studied?, and 2) How could *"Optimization of ECT"* be achieved? The following summarizes some opinions on each of these issues :

Who should be studied ?

1) Treatment-resistance. This particular type of schizophrenia takes precedence as the first group of patients to be studied urgently. Schizophrenia is one of the most critical public health problems of every country. There has been no controlled study in this area[5,6]. Clozapine therapy is the only treatment of choice in these patients, but only about 30-50 per cent of the patients will respond, and many patients are unable to take clozapine for a variety of reasons[16,17].

2) Treatment-intolerance. At the present time, there are 3 newer atypical neuroleptics, i.e. clozapine, risperidone, and olanzapine. Some patients may not be able to tolerate these drugs as well. Given the fact that most of these patients are in a low socioeconomic status, many of them could neither

Table 2. Changes in BPRS scores of the ECT responders (N = 23).

On admission (mean±SD, range)	First improvement	3-week-stabilization-period					End of Study
		R1	R2	R3	W1	W2	
44.1 ± 8.4 (37- 56)	23.1±2.7 (18-27)	17.8±2.9 (14-25)	17.9±33 (12-25)	16.5±4.6 (7-24)	18.9±6.5 (4-26)	19.5±4.6 (7-24)	19.6±6.8 (5-33)

Abbrev. : R1 = 1st regular ECT, R2 = 2nd regular ECT, R3 = 3rd regular ECT
W1 = 1st weekly ECT, W2 = 2nd weekly ECT
End of study is the period of one week after the last treatment.

complete their academic functions nor work regularly. When the cost of treatment has been taken into account, the role of ECT treatment in these patients is worth studying, especially in developing countries. The ECT study of treatment-intolerant schizophrenia must be conducted individually separate from the treatment-resistant group.

3) First-break psychosis in young adults. In this group, the cross-sectional clinical picture is often ambiguous as to the long-term course and development of the illness. The long-term use of neuroleptic exposes the patient to the unnecessary risk of extrapyramidal symptoms, including tardive dystonia and tardive dyskinesia. This approach is much less safe than the use of ECT treatment[6,18].

How could "Optimization of ECT" be achieved?

"Optimization" means both achieving the biggest clinical effect as quickly as possible with minimal side effects, and the issue of cost effectiveness. Therefore, at the present time in the current climate of focus on health care delivery, clinical optimization research is extremely important. The author discusses some critical points in research design briefly :

1) Treatment comparisons. This particular type of ECT study provides more information about the effectiveness of each treatment. But this should not be a critical element of design, as the majority of patients in the study would have received extensive and ineffective pharmacotherapy. What makes ECT work should be more important than how its effect is compared to other treatments.

2) Treatment standards. A consensus on standardization of the treatment protocols is sorely needed. This includes treatment techniques, concomitant medications, post-ECT treatment, etc. The recommendations provided by the American Psychiatric Association Task Force on ECT[19], and the Royal College of Psychiatrists' Special Committee on ECT[20] are helpful.

3) Outcome measurements. What to measure? When to measure? For how long? Standard measures should be used. The criteria for relapse must be defined clearly.

4) Sample size. A large sample size is not always required in ECT studies, if there are : 1) the same direction of change in almost all patients, 2) dramatic clinical response, and 3) good outcome measure. There may be nonspecific "noise" and prohibitive costs, unnecessarily occurring secondary to the use of too large a sample size.

5) Homogeneous group of patients. There should not be any significant differences in the clinical characteristics of the patients in each treatment arm of the comparison treatment studies. The author used a *3-week-stabilization-period* screening the patients suitable for the continuation treatment study. The stability of clinical symptoms during these 3 weeks should be ascertained so that every patient is in the same baseline condition. The first week of the stabilization period started immediately after there was clinical improvement, with the BPRS scores at that time being used as the cut-off score. During the first week, there were substantial fluctuations of the patients' clinical symptoms. Therefore, the author continued regular ECT treatments (3 treatments/week) for one week in order to minimize this discrepancy. If the patients improved progressively or did not worsen, this meant that they might respond to the ECT treatments. During the second week, these patients were tested for the stability of their clinical conditions by extending their treatment schedules to once a week. The patients who could pass the author's assessment criteria, were retested by using a weekly treatment schedule again during the third week. Therefore, the hypothesized *3-week-stabilization-period* has 3 occasions to test whether or not the patients respond to ECT treatments. The ECT responders by the author's criteria should be in the same baseline clinical condition, making them ideally suitable for the continuation treatment study.

SUMMARY

This pilot study is the first ECT study providing: 1) a response criterion, 2) a screening method to obtain an ideal sample for the continuation treatment study, and 3) proper time for termination of acute ECT treatment.

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REFERENCES

1. Carpenter WT, Buchanan RW. Schizophrenia : Introduction and overview. In : Kaplan HI, Sadock BJ, eds. Comprehensive Textbook of Psychiatry, 6th ed.,Baltimore, Williams&Wilkins, 1995: 889-902.
2. Meduna LJ. Versuche uber die biologische Beeinflussung des Abaufes der Schizophrenia : Camphor und Cardiozolkrampfe. Zeitschrift für Gesamte Neurologie und Psychiatrie 1935;152: 235-62.
3. Cerletti U, Bini L. Un neuvo metodo di shockterapie 'L'elettro-shock'. Balletino Academia Medica Roma 1938;64: 136-8.
4. Fink M. Myths of "Shock Therapy". Am J Psychiatry 1977;134: 991-6.
5. Krueger RB, Sackeim HA. Electroconvulsive therapy and schizophrenia. In ; Hirsch S, Weinberger D (ed.) : Schizophrenia. Oxford, Oxford University Press 1995: 503-45.
6. Fink M, Sackeim HA. Convulsive therapy in schizophrenia? Schizophr Bull 1996;22: 27-39.
7. Salzman C. The use of ECT in the treatment of schizophrenia. Am J Psychiatry 1980;137: 1032-41.
8. Monroe R. Maintenance electroconvulsive therapy. Psychiat Clin North Am 1991;14: 947-60.
9. Stephens S, Pettinati H, Greenberg R, et al. Continuation and maintenance therapy with outpatient ECT, In : Coffey CE (ed.) : The Clinical Science of Electroconvulsive Therapy. Washington DC, American Psychiatric Press, 1993: 143-64.
10. Fink M. Convulsive Therapy : Theory and Practice. New York, Raven Press, 1979: 306.
11. Kellner C. Defining a course of ECT (ed.). Convulsive Ther 1995;11: 229-31.
12. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. revised 3rd ed. Washington DC, American Psychiatric Association 1987.
13. Overall JF, Gorham DR. The Brief Psychiatric Rating Scale. Psychol Rep 1962;10: 799-812.
14. Train the Brain Forum Committee (Thailand). Thai mental state examination-TMSE. Siriraj Hosp Gaz 1993; 45: 359-74.
15. Sackeim HA. Continuation therapy following ECT : Directions for future research. Psychopharm Bull 1994; 30: 501-21.
16. Meltzer HY, Bastani B, Kwon KY, et al. A prospective study of clozapine in treatment-resistant schizophrenic patients. Psychopharmacol 1989; 99: 568-72.
17. Meltzer HY. Dimensions of outcome with clozapine. Br J Psychiatry 1992; 160: 46-53.
18. Kellner C. Is ECT the treatment of choice for first-break psychosis? Convulsive Ther 1995; 11: 155-7.
19. American Psychiatric Association. The practice of ECT : recommendations for treatment, training, and privileging : A Task Force Report on ECT. Washington DC, American Psychiatric Press 1990.
20. Royal College of Psychiatrists. The ECT Handbook : the 2nd Report of the Royal College of Psychiatrists' Special Committee on ECT. Gaskel, London, 1995.

การใช้ช่วงระยะคงที่ในงานวิจัยการรักษาด้วยไฟฟ้าในโรคจิตเภท†

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การรักษาด้วยไฟฟ้าได้ถูกนำมารักษาผู้ป่วยโรคจิตเภทเป็นครั้งแรกตั้งแต่ปี คศ.1938 แต่จนถึงปัจจุบันเราก็ยังไม่ทราบชัดเจนเกี่ยวกับบทบาทของการรักษาด้วยไฟฟ้าในโรคจิตเภท ทั้งนี้อาจเนื่องเพราะงานวิจัยที่ทำในโรคนี้มีไม่มาก และงานวิจัยที่มีอยู่ก็มีปัญหาเกี่ยวกับระเบียบวิธีวิจัยเป็นอย่างมาก จนไม่มีงานวิจัยงานใดที่สามารถยืนยันประสิทธิภาพของการรักษาชนิดนี้ ปัญหาของระเบียบวิธีวิจัยที่พบบ่อย ได้แก่ 1) ขาดเทคนิคที่เหมาะสมในการรักษา 2) มีความแตกต่างกันอย่างมากในลักษณะทางคลินิกของผู้ป่วยที่นำมาใช้ศึกษา และ 3) ไม่มีการวัดผลที่เหมาะสมได้มาตรฐาน

ผู้วิจัยได้คิดค้นการใช้ระยะคงที่ในการทำงานวิจัยชนิดนี้ โดยตั้งสมมุติฐานว่าการใช้ระยะคงที่ทำให้ผู้วิจัย 1) สามารถแยกผู้ป่วยกลุ่มที่ตอบสนองต่อการรักษาด้วยไฟฟ้าออกจากกลุ่มที่ไม่ตอบสนองได้อย่างชัดเจน 2) หาจำนวนครั้งของการรักษาที่เหมาะสม และ 3) กำหนดจำนวนครั้งที่เหมาะสมของการรักษาด้วยไฟฟ้า

ผลการศึกษา การใช้ระยะคงที่ในงานวิจัยการรักษาด้วยไฟฟ้าในโรคจิตเภท สามารถแยกผู้ป่วยได้อย่างชัดเจนตามวัตถุประสงค์ของผู้วิจัย หาจำนวนครั้งที่เหมาะสมของการรักษา และหาจุดตัดที่ต้องการได้ ทำให้ได้ผู้ป่วยที่มีลักษณะเหมาะสมต่อการศึกษาผลของ continuation treatment ต่อไป ผู้วิจัยได้สรุปปัญหาที่พบได้บ่อยเกี่ยวกับระเบียบวิธีวิจัยของการรักษาด้วยไฟฟ้าและแนวทางการแก้ไข.

คำสำคัญ : การรักษาด้วยไฟฟ้า, ช่วงระยะคงที่, งานวิจัยโรคจิตเภท

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