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AWARD PAPER

Efficacy of Electroconvulsive Therapy in Treatment Resistant Schizophrenia : A double-blind study

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ABSTRACT

Background : ECT, though not favoured in the West for treating schizophrenia, is regularly practiced in India for this indication, particularly in poorly responding/treatment resistant cases. Therefore, its role in treatment-resistant schizophrenia is a subject of systematic investigation.

Aim : To compare the effectiveness and safety of Electroconvulsive therapy (ECT) in a group of treatment-resistant schizophrenia patients with a control group.

Method : Eligible and consenting patients were randomly allocated to the ECT or Sham ECT groups. Both received antipsychotic drugs. Twenty-five patients completed the study (ECT, n=15; Sham ECT, n= 10). The study was conducted in a double-blind manner. Clinical change was assessed weekly with BPRS, CGI and adverse event measures. ANOVA for repeated measures and other post-hoc comparisons were used for data analysis.

Results : ECT treated patients improved significantly over successive weeks ($p<0.002$) after 6 ECTs, whereas the group receiving sham-ECT did not. In both the groups, however, CGI scores did not change significantly, suggesting a dissociated response pattern. ECT was associated with greater relief among carers and lower re-hospitalization.

Conclusion : ECT augmentation may well have a significant impact on the clinical course of patients with treatment resistance schizophrenia. It is unclear, but possible, that these changes may be reinforced and maintained by maintenance ECTs. Replication of the present investigation and further studies on maintenance ECT would be rewarding.

Key Words: Electroconvulsive therapy, Treatment Resistant Schizophrenia

INTRODUCTION

Traditionally, schizophrenia has been conceived as a behavioural syndrome characterized by early onset and chronic, unremitting course resulting in deterioration. These defining characteristics indicate that chronicity is central to the diagnosis of schizophrenia. Even in the acute phase of the illness, as high as 40% of pharmacologically treated patients continue to exhibit moderate to severe psychotic symptoms, and nearly 10% of them do not show any improvement (APA, 1994). Thus, the patients with schizophrenia are potentially chronic but therapy-resistant as well. In order to define this group, a set of operational criteria has been introduced (Kane et al, 1988).

Currently, antipsychotics drugs are considered to be the *first line* treatment in schizophrenia. Despite good compliance and adequate treatment, upto 25% of these patients remain partially or totally unresponsive to antipsychotic drug treatment (Brenner et al, 1990). They may require higher dose, switch to another antipsychotic of a different class or use of adjunctive treatments like lithium, benzodiazepines, antidepressants or ECT (Morrison, 1996).

Electroconvulsive therapy (ECT) was seen as a promising treatment for schizophrenia. Due to several reasons, it fell out of favour. It has been claimed that the results of controlled studies were negative (Taylor and Flemminger, 1980), that ECT had little influence on the course and outcome of schizophrenia and that those with chronic symptoms rarely improved. Further, neuroleptic drugs were found to be at least as effective as ECT in schizophrenia (May et al., 1976) and maintenance ECT was not shown to be effective. The strong adverse public opinion has also led to its infrequent use.

On the other hand, Christison et al (1991) opined that ECT continued to have a place in the treatment of some patients of schizophrenia and that the role of ECT for patients with chronic symptoms was less clear. Therefore, use of ECT in neuroleptic-resistant patients was debatable and that double blind controlled investigations were necessary to resolve this issue. The present study was thus designed to determine the effect of ECT in treatment-resistant schizophrenia.

MATERIAL AND METHODS

Patient selection

Forty-five consecutive OPD patients suffering from schizophrenia (DSM IV) (American Psychiatric Association, 1994) and treatment refractoriness (Kane et al., 1988) were selected for the study. Two clinicians independently (UG & UK) confirmed the diagnosis. All the patients were screened for persistent illness of five or more year's duration with no satisfactory social and occupational functioning. Where possible, it was also verified through prescriptions and hospital records that each patient had at least three periods of treatment in the preceding five years with neuroleptics of at least two different chemical classes, at doses equivalent to or greater than 1000 mg/day of Chlorpromazine equivalent for a period of 6 weeks each without significant relief. The selected patients were admitted and pre-anaesthetic assessment was done in the department of Anaesthesia.

Rating instruments

At this baseline, all the patients were administered Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962) for screening in keeping with the criteria by Kane et al (1988) and Clinical Global Impression Scale (CGI) prior to the patients being scheduled for real or sham-ECT treatment. Those with total BPRS less than 45 or CGI-S $\leq$ 4 were excluded from the study. In addition, all patients were rated on standard movement disorder rating scales (EPS and TD), visual analogue for subjective comfort with treatment as well as rater based assessment of patients' tolerability of drugs and/or ECT.

Informed consent procedure

The purpose and the design of the study were explained to the patients and the member(s) of the family, including the fact that the patient may or may not receive the ECT. Consent for general anaesthesia and ECT was obtained from the patients, or, in case the patient was unable to give consent, from a responsible member of the family. The relatives were also educated about the available treatment alternatives. The patients and the consenting relative(s) were informed that they could withdraw the consent at any point if they desired so, without adversely affecting care.

Anaesthesia and ECT procedures

All the selected patients were scheduled for ECT and were kept fasting overnight. In the ECT room, intravenous line was secured using a 22 gauge indwelling cannula on the dorsum of hand. Bitemporal leads were applied and the parameters on the ECT machine (MECTA-SR1 apparatus) were selected to deliver a brief pulse intensity of 50% to 200% of seizure threshold. After the parameters were adjusted, the psychiatrist left the room and the patients thereafter were managed by the anaesthesia team. Using a random number table, the patients were randomly allocated to treatment groups by anaesthesia team and none of the psychiatrists knew the blind.

Irrespective of the group allocation, anaesthesia was induced in all the patients with injection thiopentone 4-5 mg/Kg. The patients in the study group were administered injection succinylcholine 0.6mg/kg and were manually ventilated with 100% oxygen using face mask with Magill's circuit connected to Boyle's anaesthesia apparatus. When the neuromuscular blockade had set in, ECT was given as per the set parameters and seizures were recorded. The seizure duration was determined by the interval between the ECT stimulus delivery and the last spike in the EEG recording. To ensure seizure duration of 25 seconds, the seizures were recorded by two electrodes placed bilaterally with unipolar frontal EEG lead. In the control group, ECT was not given, however, after induction of anaesthesia manual ventilation was done till the patient returned to adequate spontaneous respiration. The patients were shifted out of the ECT room when they were conscious, breathing spontaneously and obeying verbal commands.

Antipsychotic drug treatment and rescue medications

All the patients were given chlorpromazine up to 1000 mg/day. The dose was titrated in terms of clinical response and side effects. Extrapyramidal side effects, if any, were managed by the trihexiphenedyl up to 6 mg/day. In uncontrolled agitated psychotic patients, intravenous diazepam and promethazine were also used as and when required. To facilitate compliance to the treatment regimen, the drugs were supplied free of cost.

The patients were monitored for efficacy of treatment modalities with BPRS and CGI and side effects if any were recorded.

RESULTS

Of the 45 patients who fulfilled the eligibility criterion, only 31 gave written informed consent. Five patients did not complete the study; one more patient was excluded as her diagnosis changed to schizoaffective disorder. Thus, the data of only 25 patients who completed the study were subjected to data analysis.

Both the groups received an average of about 500 mg/day of chlorpromazine equivalents at the baseline. The two groups were comparable in respect of variables such as age, sex, marital status, occupational status, socioeconomic status, education, and presence/ absence of stressor (Table 1).

TABLE 1: Sociodemographic variables in two groups (ECT and Sham ECT)

	ECT n=15	Sham ECT n=10
Age (Years)	29.8+8.54	29.1+5.7
Male	60%	70%
Female	40%	30%
Marital status	2/15	3/10
Stressor Present	20%	20%

The two groups did not also differ in respect of the clinical variables such as past history of ECT, subtype, expressed emotion in the family, body type, general assessment of functioning scale score and presence of first rank symptoms (Table 2).

TABLE 2: General clinical characteristics of two groups (ECT and Sham ECT)

	ECT n=15	Sham ECT n=10
Past h/o ECT	2	Nil
Insidious onset	53%	70%
Mean duration of illness	7.6 years	6.9 years
Age of onset	22.13+7.3 years	22.2+4.8 years
EE (Present)	46.6%	60%
GAF score	25.53	26.4
FRS	60%	80%

EFFICACY

Primary measure: Total BPRS **(see Table 3 for details)**

In the present study, 18 items BPRS was used; each item was rated on a scale of 1 to 7. Out of the maximum possible score of 126, a score of 45 or more was considered to be of the inclusion criteria in the trial. Improvement was defined as a 20% decrease in BPRS total score plus either post treatment CGI rating mildly ill (≤3) or a post treatment score of 35 or less on BPRS.

Since the patients were assessed at baseline and later weekly, we analysed the data set using ANOVA for repeated measure (ANOVA – RM) to evaluate the weekly change on BPRS.

TABLE 3: Total BPRS from baseline till week 4 between ECT and Sham-ECT groups of patients

Groups	Observation on the BPRS for consecutive 4 weeks				
	Week 0	Week 1	Week 2	Week 3	Week 4
Group I	55 ± 7.2	52.6 ± 7.8	48.6 ± 7.9	47.6± 8.6	44 ± 7.6
Group II	50.1 ± 3.9	45.6 ± 5.8	42.6 ± 7	42.2 ± 8	40.4 ± 10

The ECT group has shown significant decline of scores on BPRS as seen in Table 3 (ANOVA – RM; MS between groups=247.7; MS within groups=61.6; F=4.5; d.f.= 4, 74; p<0.002). Similar comparison in the sham-ECT group does not reveal any significant difference (ANOVA–RM; MS between groups=45.9; MS within groups=63.2; F=0.72; d.f.=3, 39; p>0.542). Further post-hoc comparisons across the weeks reveal that the improvement occurs with effect from the second week, after 6 ECTs are administered.

Secondary Measures: Clinical Global Impression (CGI) (Table 4)

Table 4 shows total CGI between baseline and week 4 in ECT and sham-ECT groups of patients. There are no significant differences between the groups.

TABLE 4 : Total CGI between baseline and week 4 in ECT and sham-ECT

Group	Baseline	Week 4	p
ECT	4.9	4.13	NS
Sham-ECT	4.6	3.8	NS

Other secondary measures included rescue medication, total daily antipsychotics received, subjective satisfaction with the treatment received. The two groups received comparable doses of rescue drugs, i.e., parenteral diazepam or promethazine. Their daily oral Chlorpromazine equivalents were also comparable. However, the relatives favoured ECT treatment for greater comfort and satisfaction. Finally, the rates of re-hospitalization were lower for ECT group (20%) as opposed to sham-ECT (70%).

Discussion

The principal finding of this study is that ECT-treated patients improved significantly on BPRS from week 2 onwards. There has been a case report of ECT augmenting Clozapine in treatment resistant schizophrenia, after the effect of the latter appeared to have been lost (Safferman and Munne, 1992). These authors found that the combination of ECT and Clozapine was safe and effective and suggested that further controlled studies were required to work out the precise role of the combination in the context of treatment resistant schizophrenia. The present investigation is an important step in that direction. Hopefully, this might stimulate independent replication elsewhere.

In his review, Meltzer (1992) justifiably listed ECT as a treatment modality for therapy-resistant schizophrenia. A positive treatment effect of ECT in two clozapine unresponsive schizophrenic patients was described by Sajatovic and Meltzer (1993). Our study provides objective evidence that indeed ECT would favourably influence the psychopathology of treatment resistant schizophrenia patients. It is unrealistic to expect an immediate response with ECT. Clearly, the changes are detected after the 6th ECT, at the completion of second week.

The sham-ECT group did not have any significant symptom change. Hence, we would restrict further discussion to the ECT group.

Many studies in the past, if only in the context of treatment of schizophrenia, have reported similar treatment effects on the BPRS (Aggarwal and Winny, 1985; Abraham and Kulhara, 1987; Sajatovic and Meltzer, 1993).

The BPRS data favour the argument that ECT did have an augmenting effect on the ongoing neuroleptic drug therapy, at least transiently. Since the study had a design of random allocation of patients to treatment groups and is conducted double blind, the ECT-group would not have improved if they continued to receive drugs alone. While discussing their results of uncontrolled, open trial of ECT, Sajatovic and Meltzer (1993) had observed, *"...the possibility that ECT procedure including anesthesia may have contributed to the improvement can only be studied with a sham-ECT control group."* The present study has accomplished just this mission.

In a study like this, schizoaffective patients are better avoided (Janakiramaiah and Subbakrishna, 1981). Affective symptoms (DSS) in schizophrenia may predict good outcome (Salzman, 1980; Wells, 1973). However, Sajatovic and Meltzer (1993) maintained that the improvement had not been simply attributable to improvement in mood symptoms. Even Dodwell and Goldberg (1999) failed to notice any therapeutic edge of ECT in schizoaffective

disorder. In the present study, we stayed clear of the schizoaffective disorder to avoid any noise.

A close look at CGI data would indicate that the clinical problem of schizophrenia, apparently, persists, beyond symptom resolution. Of course no clinician expects massive treatment effect of any agent on *this* group. These patients are chronically ill and drug treatment alone cannot take care of the deficits. One can expect, however, to detect a definite but small magnitude of clinical change. If the schizophrenia group treated with ECT did not improve in the first place, it would be unwise to pursue this research any further.

Clinicians would readily agree that a course of 12 to 18 ECTs would not restore most of these therapy resistant cases to normal or near normal in psycho-social functioning. For this to happen, one would have to combine non-pharmacological approaches, including behaviour modification and cognitive therapy. In addition, one has to work with the families and significant others for effective intervention of negative emotional climate. However, we have two patients whose CGI came down on 3 or less. It indicates the possibility that ECT treatment, in a significant minority, would produce a faster relief than expected. Again, a large sample would be able to detect this change.

The secondary measures include: family's acceptance of the treatment and frequency of re-hospitalization. Our data suggests that only 20% of cases that received ECT were re-hospitalized within 6 months, as compared to 70% in the sham-ECT group. A larger sample size would have ensured a more robust treatment effect. It would be interesting to compare the levels of extrapyramidal side effects between the two groups. There is some evidence suggesting that patients treated with ECT may experience less EPS (Goswami et al, 1989).

ECT was a well-accepted treatment as rated by the patients' relatives. It is possible that there is a cross-cultural variation in public perception and sensitivity. ECT and clozapine are both difficult choices to make in India. Several factors may render ECT as an attractive treatment alternative: 1) lack of long term side effects, 2) lower dose of concomitant neuroleptic medication, 3) reduction in the duration of hospital stay and 4) cost.

Social dimensions of change are linked to the higher level of acceptance/comfort of the relatives associated with ECT. In short term analysis, more than this would not be realistic. An independent replication and the follow up information on this issue are vital to the state of ECT research in the context of treatment-resistant schizophrenia.

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