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The Nottingham ECT Study

A Double-Blind Comparison of Bilateral, Unilateral and Simulated ECT in Depressive Illness

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Summary: Sixty nine patients took part in a double-blind study to investigate the efficacy of bilateral, unilateral, and simulated ECT in the treatment of depressive illness. The findings suggest that both bilateral and unilateral ECT are highly effective treatments for depression and are significantly superior to simulated ECT. There was also evidence that patients receiving bilateral ECT recovered more rapidly than those receiving unilateral ECT and required significantly fewer treatments. The relevance of these findings to clinical practice is discussed.

ECT has been shown by several studies to be a highly effective treatment in severe depressive illness (Fahy *et al*, 1963; Greenblatt *et al*, 1964; MRC Study, 1965; McDonald *et al*, 1966; Wilson *et al*, 1963, but these had methodological weaknesses, and it was not until 1978 that studies using more rigorous methodology were published. Four utilised a double-blind placebo-controlled design (Brandon *et al*, 1984; Freeman *et al*, 1978; Johnstone *et al*, 1980; Lambourn & Gill, 1978) and one, a double-blind cross-over design (West, 1981). Lambourn & Gill (1978) used brief pulse stimuli applied to non-dominant temporo-parietal electrodes in one group of depressive patients, and simulated ECT in a matched second group. Both groups of patients did well, and the study failed to demonstrate more than a trend in favour of ECT. In the Northwick Park study of similar design but utilising the more traditional sinusoidal stimulus waveform applied to bilateral electrodes, Johnstone *et al*, (1980) demonstrated a significantly superior effect for real ECT, but also a remarkably high placebo effect in the simulated ECT group. In fact, ECT seemed to have only a small therapeutic effect on depression at the end of the trial period. These studies challenged the status of ECT and the paramount importance of the convulsion, whilst reopening the controversy surrounding the relative efficacy of different techniques. The other recent studies by Freeman *et al* (1978), West (1980) and Brandon *et al* (1984) have shown greater improvement in those patients given a full course of bilateral ECT, compared with a simulated ECT group.

This present study replicates the methodology used in both the Lambourn & Gill and the Northwick Park studies, and for the first time, compares bilateral, unilateral, and simulated ECT. It was hoped that this would resolve the unilateral bilateral controversy as well as determining the efficacy of ECT.

Method

Between August 1981 and February 1983, 564 patients were admitted to Mapperley Hospital, Nottingham, with an ICD-9 diagnosis of depressive illness. Mapperley Hospital serves the city of Nottingham and at the time of the study, provided the only in-patient facility for patients under 65 from the city and its immediate environs. Of these, 234 were referred for ECT, but not all the responsible medical practitioners gave consent for their patients to enter the study: 118 patients were seen and assessed for their suitability to enter the ECT study. Those right-handed informal patients who met the Medical Research Council (1965) criteria for depressive illness of greater than one month duration, who did not have a severe physical illness, and who had not already received ECT for this episode of illness, were asked for their consent to take part in the study. All patients who gave consent were randomly assigned to one of three groups of bilateral ECT, right unilateral ECT, or simulated ECT, and treatment was administered twice weekly, following the usual hospital procedures. During the study, patients were allowed to receive small doses of benzodiazepines. Patients received 1.2 mg of intramuscular atropine half an hour prior to treatment, and a standardised anaesthetic regime (modified for extremes of physique) of methohexitone sodium, 70 mg and suxamethonium bromide, 50 mg given intravenously. The ECT machine used was the Ectron Duopulse Mark IV, waveform 1, which was checked monthly by the Medical Physics Department. In the bilateral group, electrodes were placed in the bi-temporal position; in the unilateral group, they were applied to the right temporo-parietal position (Lancaster *et al*, 1958). Patients in the simulated group received the whole ECT procedure, but no shock. The cuff method was used to monitor the occurrence of a fit. The fit was timed, using a stop-watch. The rater and clinical teams in charge of patients were blind to the treatment group. The number of treatments given was decided by the clinical team in charge of the patient.

At the initial assessment, a standardised psychiatric history was taken, and all patients were assessed using: (1) MRC criteria for major depressive illness; (2) the Present State Examination (PSE, Wing *et al*, 1974); (3) some behavioural items from the Psychological Impairments Rating Schedule (PIRS, Wing *et al*, 1974); (4) the Montgomery & Asberg Depression Rating Scale (MADRS, Montgomery & Asberg, 1979); and (5) the Hamilton Depression Rating Scale (HDRS, Hamilton, 1960). Handedness was decided using the Annett Handedness Questionnaire (Annett *et al*, 1974). Study patients were seen after every two treatments, within two days of the last ECT, but not on a treatment day, and rated using the MADRS. Within a week of the end of study treatment and before commencing any other treatment, patients were rated using the PSE (with a one week time-scale), the PIRS items, the MADRS, and the HDRS. Full details of the PSE findings will be described elsewhere. At one, three, and six months after treatment, patients were rated again, using the PIRS items, the MADRS and the HDRS. Further ECT in the follow-up period was recorded and a record was kept of all medication given before, during and after the study treatment. A global assessment of change in depression, based on the opinion of the clinical team in charge of the patient, was recorded for all the patients initially seen, regardless of whether they entered the study or not.

Results

Of the 118 patients initially assessed, 69 fulfilled the entry criteria for the study. Reasons for failure to enter the study were: the patient refused consent (5), the consultant refused consent (22), patient detained under a section of the Mental Health Act (9), and others (e.g. significant physical illness, 13). The group of patients entering the study was compared with the group not entering the study, to determine whether the groups differed significantly from one another in age, sex, initial scores on the MADRS, HDRS, PIRS, presence of delusions, anxiety or agitation, length of present episode, previous treatment, previous illness and family history. A similar comparison was made between the three groups entering the study, each of which contained 23 patients. The statistical tests used included student's *t*-test (two tailed), chi-square, and one-way analysis of variance with Scheffe's Multiple Range Test (AOVS) for the continuous variables. These comparisons failed to show any significant differences prior to the start of treatment.

During the study, 51 patients received benzodiazepines; the mean daily dosage was equivalent to diazepam 11.12 mgs in the bilateral group, 13.75 mgs in the unilateral group, and 15.00 mgs in the simulated group. These amounts are not significantly different. Some patients, prior to entering the study, were on drugs which the clinical teams in charge did not feel ethically able to stop. These drugs included lithium in three patients, a major tranquilliser in one, and an antidepressant in one.

A convulsion was satisfactorily achieved on application of the electroconvulsive stimulus (ECS) in both the bilateral and unilateral groups. It was, however, necessary to apply a second ECS on seven occasions in the unilateral group, but on only one occasion in the bilateral group. There was no significant difference in the mean fit length between these two groups. There were no significant differences in mean dosage of anaesthetic and muscle relaxant in the three groups.

Of the 69 patients entering the study, 25 received fewer than six study treatments; these were classed as withdrawals. In the simulated group, seven patients were withdrawn by their consultants for failure to improve or because they became physically ill, and in one case it became necessary to detain the patient on a section. In the unilateral group, five patients were withdrawn because of failure to improve, one patient was better, and one withdrew consent. In the bilateral group, two patients were withdrawn for failure to improve, four were better, two withdrew consent, and one became physically ill.

TABLE I

Change in scores before and after treatment (percentage change in brackets)

	Simulated ECT group	*Unilateral ECT group*	*Bilateral ECT group*
MADRS	8.70 (75.29)	24.00*** (30.61)	24.76*** (22.35)
HDRS	13.90 (65.51)	30.53** (29.33)	28.00** (26.76)
PIRS	2.55 (32.94)	6.89* (24.06)	5.71* (31.39)
Number on whom complete data available	20	19	21

*$P<0.05$ **$P<0.01$ ***$P<0.001$

The scores on the MADRS were used to compare the three treatment groups; the scores after the first six study ECTs, and one, three, and six months after ECT are shown in the Figure. The results were analysed using AOVS on the changes in the MADRS scores. The significance levels shown refer to the simulated versus the unilateral group and to the simulated versus the bilateral group. There were no significant differences between the unilateral and the bilateral groups in this analysis.

The scores on the MADRS before treatment were then compared with the scores after two, four and six study ECTs or at the end of the study treatments. These results were analysed using Student's *t*-test (two-tailed), and show that whilst the improvement was highly significant ($P<0.001$) for the two electricity groups from as early as after two ECTs and maintained after four and six ECTs, there was also a statistically significant change in the simulated group ($0.001<P<0.045$) at the end of the study treatments.

The changes in score between the beginning and end of treatment, as measured on the MADRS, HDRS, and PIRS, were then analysed using AOVS in patients who were not withdrawn from the study and in those who received greater than or equal to four study ECTs before being withdrawn. The results are shown in Table II, where the significance levels refer to the simulated compared to the unilateral ECT group, and the simulated compared to

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TABLE II

Significance levels for differences in total number of ECT given

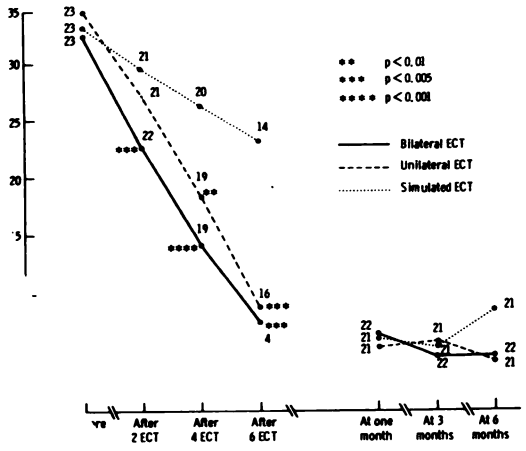
Simulated ECT group	*v.*	Unilateral ECT group	$P = 0.013$
Simulated ECT group	*v.*	Bilateral ECT group	$P < 0.001$
Unilateral ECT group	*v.*	Bilateral ECT group	$P = 0.05$

(Total number of ECT given including study ECT and extra ECT given in the month after the study:—Simulated ECT group 9.64, Unilateral ECT 7.91, Bilateral ECT group 6.59).

the bilateral ECT group. There were no significant differences between the unilateral and the bilateral ECT groups.

After the patients completed the study, 32 went on to receive further bilateral ECT. When analysed by treatment group, the mean number of additional ECT given in the simulated group was 4.14; in the unilateral group 2.18; and in the bilateral group 0.91. In order to investigate the relevance of these findings, the number of ECT given in the study was added to the additional number given, and AOVS was then performed on the logarithm of these numbers. (The logarithm was used as the distribution was skewed). The results show that there were significant differences between each of the three treatment groups with least treatment given in the bilateral group.

An analysis of change and percentage change scores was then performed on the MADRS, HDRS, and PIRS scores which were obtained one, three, and six months after the end of treatment. For this analysis, all patients who entered the study and on whom follow-up data are available were included. There were no significant differences. No significant differences were found in the number of ECT given, or other physical treatments given in the rest of the follow-up period, from one to six months after the study.



Discussion

A criticism frequently made of ECT studies is the extent to which the patients are representative of those who receive this treatment in normal clinical practice. In our study, 41.5% of patients admitted to Mapperley with depression received ECT, a figure which accords closely with normal clinical practice at that hospital. This may be compared with 90/104 (86.5%) of all patients admitted with depression in the Northwick Park Study (Johnstone *et al* 1980). Only right-handed patients were accepted, so that all those entering the study were then eligible to receive any of the three study treatments.

Of patients who received ECT for depressive illness during the study period, 50.4% were assessed, and there were no significant differences between those who entered the study and those who did not. However, a number of patients were not assessed, so that we are not able to exclude the possibility that the sample was biased. The patients entering the study were randomly assigned to the three treatment groups, and there were no significant differences between these groups. The random allocation was therefore successful in forming three equally depressed groups of patients.

Some critics have doubted the validity of assessing the occurrence of a fit following an ECS in the absence of EEG monitoring (Brumback, 1983). However, Christenson & Koldbaeck, (1982) and Fink & Johnson (1978) have shown that the cuff method underestimates rather than overestimates the occurrence of a fit, as compared with EEG monitoring.

Bilateral and unilateral ECT were both highly significantly better than simulated ECT, using either MADRS, HDRS or PIRS scores, or percentage change scores. These results confirm the findings of previous studies (Brandon *et al*, 1984; Freeman *et al*, 1978; Johnstone *et al*, 1980; West, 1981). All these studies found a significant difference between bilateral and simulated ECT. The difference in our study was not maintained at one, three, and six months after treatment, although the improvement persisted. The Northwick Park study also found that there was no difference between the groups by one month after their study. However, in the present study, many patients in the simulated group went on to receive furthr ECT in the month after the study, and many patients in all three groups received antidepressants. Very few patients in any of the three groups went on to receive further ECT between one and six months after the study, but this cannot be regarded as evidence that ECT

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has a prolonged effect, since so many patients were receiving antidepressants.

There were no significant differences in overall outcome using the MADRS, HDRS, or PIRS change or percentage change scores, between the bilateral and unilateral groups. However, when speed of response is considered, the bilateral group was significantly superior to the simulated group after two treatments, whereas the unilateral group did not become significantly superior to the simulated group until after four treatments. This may indeed mean that unilateral ECT produces a slower response than bilateral ECT—an argument which is strengthened when the reasons for withdrawal from the two electricity groups are analysed. Five patients in the unilateral group were withdrawn for failure to improve, compared with only two in the bilateral group. On the other hand, whilst only one patient in the unilateral group was withdrawn because they were better, four were withdrawn for this reason in the bilateral group. These reasons for withdrawal would have minimised any difference in apparent response between the two groups. In addition, when the total number of ECT given is considered, (the number of study ECT together with the number of ECT given in the month after the study), the unilateral group received a mean of 7.91 treatments, compared to a mean of only 6.59 in the bilateral group. This difference may be smaller than the actual difference between unilateral and bilateral ECT, since the extra post-study ECT given were all bilateral. Our findings, therefore, do not confirm the conclusion of D'Elia & Raotma (1975) that unilateral and bilateral ECT have equivalent therapeutic efficacy. They do confirm the findings of Abrams *et al* (1983) that bilateral ECT is more effective than unilateral. They are also in agreement with Heshe *et al* (1978) that bilateral ECT was significantly better than unilateral ECT at one week.

An earlier study, (Lambourn & Gill, 1978), produced different findings from this and from other double-blind placebo-controlled studies of ECT. At that time, one of the present authors found that a significant difference between six unilateral and six simulated ECT in depressive illness could not be demonstrated, despite satisfactory methodology. Our present findings, which suggest that unilateral ECT takes longer to produce a response and requires a greater number of treatments, may partly explain this discrepancy, although there may also have been differences in the selection of patients. The different ECS used may also be relevant. Valentine *et al* (1968) found no difference in efficacy between sine wave and brief pulse stimuli, but recent authors have disagreed. Robin & De Tissera (1982) found that higher energy stimuli had a better therapeutic effect, despite the length of the seizure which was induced being equivalent.

We have found that the passage of electricity is an important part of the ECT procedure. Both bilateral and unilateral ECT are highly effective, but unilateral requires more treatments, and the speed of response is probably slower than that of bilateral. The reasons for these differences remain a matter for speculation, but both procedures produced an adequate convulsion. It is possible that the form of ECS used is relevant to the disparate findings of various ECT studies and that there may be a specific sub-group of patients who do not respond to unilateral ECT (Price, 1981). In the absence of further knowledge, the clinical choice of bilateral or unilateral ECT must remain a delicate balance between the need for a quick response and the undoubtedly greater memory impairment produced by bilateral ECT (Fromm-Auch, 1982; Squire & Slater, 1983).

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