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THE NORTHWICK PARK ELECTROCONVULSIVE THERAPY TRIAL

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Summary 70 patients with endogenous depression, defined by strict criteria, who fulfilled the Newcastle indications for electroconvulsive therapy (ECT) were randomly allocated either to a course of eight simulated ECTs or to a course of eight real ECTs. The improvement in terms of psychiatrists' ratings in the group of patients given real ECT was significantly greater ($p < 0{\cdot}01$) than that in those given simulated ECT, but the difference between the two groups was small in relation to the considerable improvement of both groups over the 4-week treatment period. No differences were found between the two groups at one-month and six-month follow-up. The therapeutic benefits of electrically induced convulsions in depression were of lesser magnitude and were more transient than has sometimes been claimed. In the real-ECT group memory was impaired during treatment but memory tests revealed no difference between the groups at six-month follow-up.

Introduction

ELECTROCONVULSIVE therapy (ECT), introduced by Cerletti and Bini[1] over 40 years ago, has been a major treatment of severe depressive illness. The antidepressant efficacy of the whole procedure is well established[2,3] but, although the convulsion is often held to be a critical element, the evidence that this is so is slender. Cronholm and Ottosson[4] found that 46 depressed patients treated with electrically induced convulsions improved more than 23 patients in whom the convulsions were shortened with lignocaine, but the treatments were not allocated at random. Robin and Harris[5] reported that a group of 15 depressed patients treated with ECT and placebo tablets did significantly better than 16 patients treated with "pseudo-ECT" (an anaesthetic with no shock) and imipramine. Other workers,[6,7] treating diagnostically mixed groups of patients, found that the addition of electrically induced convulsions offered no advantage over the administration of anaesthesia alone. This issue has lately attracted attention. Freeman et al.[8] presented data which suggested that a course of bilaterally applied ECT which began with two pseudo-ECTs effected significantly slower improvement than a course which included real ECTs from the first treatment. On the other hand, Lambourn and Gill[9] reported that depressed patients improved as quickly with six sessions of pseudo-ECT as with six real unilateral treatments.

The present study concerned 70 patients diagnosed by well-defined criteria as having endogenous depression and randomly allocated either to eight real or to eight pseudo ECTs. The mental states of the patients were assessed, by psychiatrists who were unaware of the treatment allocation, throughout the course of treatment and again one month and six months after completion of the course.

In addition to the question of the role of the convulsion in the efficacy of ECT, possible short and long term effects of the convulsion upon memory are of considerable interest. This topic has received substantial study[10] but the effects of ECT have been hard to disentangle from those of change in mood.[11] The present study provided an opportunity for clarifying this issue. Memory was tested before and during the study and at the six-month follow-up.

Method

From the results of previous studies of depressed patients with the Hamilton[12] depression scale it was calculated that a sample of 70 patients would be adequate to clarify the question of whether or not the convulsion is an important element in the therapeutic efficacy of ECT. The patients were selected from those aged 30–69 years who required inpatient treatment for depressive illness and were admitted to Northwick Park Hospital under the care of the participating psychiatrists. After admission, the Present State Examination[13] was conducted and the following criteria for inclusion in the trial were applied: the MRC[3] criteria for depressive illness (modified by the extension of the age range to 30–69 years); the Feighner[14] criteria for primary depressive illness; the Newcastle[15] criteria for endogenous depressive illness; and the Newcastle[15] criteria for predicting a good outcome from ECT. Patients who fulfilled these criteria were asked for consent to ECT and inclusion in the trial. Relatives' consent was also obtained. In those who consented the risk of anaesthesia was assessed by the anaesthetist concerned and if this was thought to be increased the patient was excluded. Patients were entered in the trial until the target figure of 70 cases was reached. During this time 109 depressed patients of appropriate age were admitted. Of the 39 who were not included 2 were detained under the Mental Health Act, 6 were regarded as poor anaesthetic risks, 4 refused ECT, 8 refused to participate in the trial, and in 19 the characteristics of the illness did not meet the criteria.

Having been included in the trial patients were allocated, for the purpose of randomisation, to separate groups according to the

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presence or absence of delusions, agitation, or retardation. The allocation of the treatments was known only to the psychiatrist who administered the ECT and to the anaesthetist. Neither of these doctors was involved in the care or assessment of the patients. The assessments used were the Hamilton[12] depression ratings, the Leeds[16] scales for depression, and the nurses' rating scales devised by Bunney and Hamburg.[17] The Hamilton ratings were conducted by one of the two consultant psychiatrists and were done before the course of ECT, weekly throughout the course, and one month and six months after completion of the course. The patients were asked to complete Leeds[16] scales at the same time. The treatments were given on Tuesdays and Fridays. Patients who began their course of ECT on a Tuesday were rated on five consecutive Mondays and those who began their course on a Friday were rated on five consecutive Thursdays. The mean time between admission and the start of ECT was 9·4 days. After the first four treatments a third psychiatrist independently assessed the advisability of continuing with the study. All the patients were treated as inpatients in the research ward of the psychiatric unit at Northwick Park Hospital.

Both groups of patients received methohexitone 1·5 mg/kg, atropine 0·6 mg, and suxamethonium 0·5 mg/kg. No electricity was passed in the simulated ECT group but in the real ECT group electrodes were placed in the bifrontal position and a current of 150 V duopulse wave form 1 was passed for 3 s. To allow confirmation that a convulsion had taken place a sphygmomanometer cuff inflated above arterial pressure was applied to one arm. In this way the convulsion could be observed unmodified by muscle relaxants. No other antidepressant treatment was given. All patients had a benzodiazepine hypnotic every night during the trial and if additional sedation was necessary diazepam was prescribed.

Memory tests were conducted by psychologists who, like the clinical investigators, remained blind to the allocation of the treatments until all the six-month follow-up assessments had been completed. This selection of tests was intended to assess both the immediate and the possible long-term effects of ECT.

After the eighth treatment the Hamilton[12] and Leeds[16] ratings were completed and the patients were then treated as the consultants in charge of them thought fit.

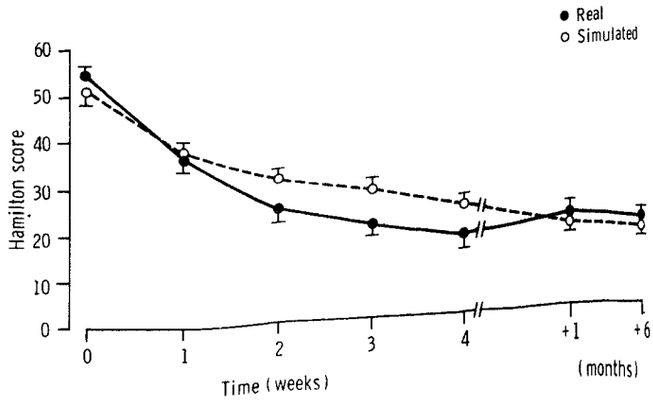
Results

General

The sample consisted of 52 females and 18 males of mean age 49·4 years. 46 patients had had definite previous episodes of depressive illness and 7 had had definite previous episodes of mania. 15 patients had received ECT for a previous episode. 49 patients had had antidepressants prescribed for the index episode before admission to the trial. 62 patients completed the full course of eight treatments. Of the 8 patients who did not, 4 (3 on simulated ECT, 1 on real) were withdrawn because of failure to progress; 1 on real ECT was withdrawn because he had a minor vascular incident involving his retina; 2 (1 on real ECT and 1 on simulated) withdrew consent to ECT; and 1 (on real ECT) became manic. Of the 62 patients who finished the course 18 (8 on real ECT and 10 on simulated) were given benzodiazepines, mainly either as diazepam 5 mg regularly thrice daily or as diazepam 10 mg in occasional doses to relieve distress. Improvement scores were similar in patients with and without diazepam. The only other psychotropic medication was a benzodiazepine hypnotic prescribed for all patients. No antidepressant medication was given during the trial. 57 of the 62 patients who completed the course were seen one month and six months later.

Outcome Assessed by Clinical Ratings

Patients in both groups improved considerably during the course of the treatment but the improvement was greater in the real-ECT group. The advantage of real over simulated ECT was not retained and at the one-month and six-month follow-ups the Hamilton[12] scores of the two groups were almost the same (see figure). The Leeds[16] self ratings showed similar trends but these were never significant, and this was also true of the ratings by nurses using the Bunney and Hamburg[17] score.



Severity of depression in relation to the course of ECT and one and six months thereafter.

The effects of ECT were assessed by analysis of variance at the end of treatment and one month and six months after completion of treatment. The tests ask whether the two groups (real or simulated ECT) differ significantly in terms of mean improvement at each time of assessment. At the end of week 4—i.e., after eight treatments—this effect is significant ($F [1,54] = 7·8$, $p < 0·01$) but at one month ($F [1,51] = 0·1$,NS) and six months ($F [1,49] = 0·4$, NS) there was no difference between the groups.

The patients' treatment ceased to be determined by the rules of the trial after the rating which immediately followed the course of real/simulated ECT. When the one-month and six-month ratings were done the patients had been on various treatments as dictated by their clinical condition. The treatments given to the two groups of patients during this time were very similar (table I) and it is not possible to attribute the loss of the advantage of real ECT to differences in the subsequent treatment of the two groups. In order to check the blindness of the study the investigators guessed which treatment they thought the patients were having. The accuracy of these guesses was no better than that predicted by chance.

TABLE I—TREATMENT IN MONTH AFTER COMPLETION OF COURSE OF TRIAL ECT

Treatment	No. of patients receiving treatment	
	Real	Simulated
ECT	1	2
Tricyclics	16	13
Other antidepressants	1	4
Anxiolytics	9	7
Lithium	1	2
Nil	3	2

Results of the Memory Tests

These will be dealt with in detail in another publication and are only referred to briefly here. Memory deficits were clearly demonstrated in the real ECT group during the course of the

TABLE II—RESULTS OF MEMORY TESTS BEFORE, DURING, AND AFTER THE COURSE OF ECT

Test	No. of patients		Before treatment		During/after treatment		6 mo follow-up	
	Real ECT	Simulated ECT	Real ECT	Simulated ECT	Real ECT	Simulated ECT	Real ECT	Simulated ECT
Subjective memory (% of patients complaining)	18	9	70	68	62	38	38	26
Concentration	16	20	62	80	67	56	50	32
15 min vigilance task (% of patients missing signals)	20	19	76	74	57	32*	—	—
Word list recall (words out of 20)	20	19	7·2	8·0	6·5	8·3	8·7	
Non-verbal recall score (complex line drawing)	17	23	—	—	9·1	20·2†	—	—
Learning labels for faces: learning score	29	28	—	—	2·6	4·6‡	5·0	5·2
Long-term memory (sentence comprehension time)	26	27	—	—	2·4	3·6§	—	—
Long-term memory (discrimination of names from the past)	14	12	2·16	2·08	—	—	2·08	2·09

*$\chi_1^2 = 2{\cdot}8$ ($p < 0{\cdot}10$); †$F(1,36) = 16{\cdot}1$ ($p < 0{\cdot}01$); ‡$F(1,53) = 5{\cdot}2$ ($p < 0{\cdot}05$); §$F(1,45) = 6{\cdot}4$ ($p < 0{\cdot}05$)

treatment but there was no evidence of persisting memory impairment at the six-month follow-up (table II). For this comparison patients who received ECT at any time other than during the trial were excluded.

Discussion

Although significant differences were established for only one of the three methods of rating used, the findings show that electrically induced convulsions do enhance the rate of recovery from an episode of depression. The findings differ in important respects from those of both Freeman et al.[8] and Lambourn and Gill,[9] although in terms of initial Hamilton[12] scores the patients in these studies had depression of similar severity to those participating in ours. Thus in a series of 70 patients treated with a course of eight bilateral real or simulated ECT over 4 weeks we found a significant effect of the convulsion while Lambourn and Gill,[9] using six unilaterally applied real or simulated treatments given over 3 weeks in 32 patients, found none. On the other hand Freeman et al.,[8] studying a group of 40 patients, reported that significant improvements could be detected on some rating scales after two real as compared with two simulated ECTs. In our larger series no significant difference was found after two treatments. In the study of Freeman et al.[8] clinicians seem to have been able to detect group differences at the end of the course of treatment and gave significantly more ECT to the group of patients in which the initial two treatments were simulated. By contrast, the clinicians responsible for our patients (who, unlike those in the study of Freeman et al.,[8] received no antidepressants during the 4-week course of the treatment trial) gave similar amounts of antidepressant therapy to the two groups of patients after the trial period (table I).

While our trial reveals a significant advantage ($p < 0{\cdot}01$) for the electrically induced convulsions, the size of the difference between the two groups is not large. The group receiving real ECT showed a mean improvement of 38·1 (SE 3·0) points on the Hamilton scale over the 4 weeks of the trial while those receiving simulated ECT showed a mean improvement of 28 (SE 2·7) points.

The most striking finding is that the differences which were present at the end of the course of eight treatments had disappeared one month later and were undetectable also at six months (figure). Although the use of antidepressant treatments (including ECT) during the follow-up period was not restricted by the trial design there were negligible differences between the groups in the extent to which such treatments were considered necessary. The findings of this study offer no support for the view that the benefits of repeated convulsions are substantial and long-lasting; they indicate that the benefits lie in speed of response rather than in long-term outcome. Because both our treatment groups had general anaesthesia we cannot assess the extent to which this, either by pharmacological or by psychological mechanisms, may contribute to the previously reported advantages of the ECT procedure over other antidepressant regimens.[2,3] Moreover, since no antidepressant-drug treated group was included, we cannot assess the question of whether optimal drug treatment can achieve as rapid a response as that seen with eight episodes of anaesthesia either with or without a convulsion.

Although these results indicate that electrically induced convulsions offer less benefit in terms of antidepressant effect than has sometimes been thought, they also indicate that such convulsions are not as harmful as has been supposed. Subjective accounts have indicated that some patients experience persisting impairments,[18] but in our wide-ranging series of tests no differences were established at six months between the real and the simulated ECT groups, who had at that time very similar ratings on the Hamilton[12] scale. We thus found no evidence that a series of eight electrically induced convulsions gives rise to lasting memory impairment but we can make no comment of the effect of larger amounts of ECT.

In conclusion, our findings suggest that the antidepressant effects of repeated electrically induced convulsions are of relatively short duration. No lasting effects upon memory were detected. The results confirm that many depressive illnesses although severe may have a favourable outcome with intensive nursing and medical care even if physical treatments are not given.

This trial was conducted under the auspices and according to the rules of the Ethical Committee of Northwick Park Hospital and with the advice of the Drug Trials in Psychiatry Subcommittee of the Medical Research Council under the chairmanship of Prof. M. Shepherd. We thank sisters I. Crichlow and G. Andrews, charge nurses M. Howell and C. Morris, staff nurse V. Palmer, and the nursing staff of Eastlake Ward, Northwick Park Hospital, who

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ALLOGENEIC BONE MARROW TRANSPLANTATION USING STEM CELLS FRACTIONATED BY LECTINS: VI, IN VITRO ANALYSIS OF HUMAN AND MONKEY BONE MARROW CELLS FRACTIONATED BY SHEEP RED BLOOD CELLS AND SOYBEAN AGGLUTININ

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Summary A procedure was developed for the isolation from human bone marrow of a cell fraction enriched for haematopoietic precursors and depleted of T lymphocytes. T cells are eliminated from bone marrow by rosetting with sheep red blood cells, followed by differential agglutination of residual T lymphocytes in the non-rosetting population by the lectin, soybean agglutinin. The fraction unagglutinated by the lectin contains a high proportion of colony-forming cells and non detectable T cell alloreactivity in vitro. Similar results were obtained with monkey bone-marrow cells, suggesting that monkeys can be used for evaluation of this fractionation technique for bone-marrow transplantation across histocompatibility barriers.

Introduction

IN the past decade, marrow transplantation has emerged as a promising curative approach to the treatment of lethal congenital immunodeficiencies,[1] aplastic anaemia,[2] and leukaemia.[3] At present, a marrow transplant can be used only for the minority of patients who have a suitable donor, matched for determinants of the HLA system, since transplants from HLA-histoincompatible donors commonly induce lethal graft versus host disease (GvHD).[4] However, results in rodents suggest that lethal GvHD can be avoided if, before administration, the histoincompatible marrow graft is depleted of alloreactive T lymphocytes.[5-8]

In earlier work, Reisner et al. showed that the plant lectin soybean agglutinin (SBA) binds to the B lymphocytes and haematopoietic precursors in the marrow and spleen of the mouse, and does not bind to T lymphocytes in these tissues.[8,9] Marrow or spleen cells could thus be fractionated by agglutination with SBA and differential sedimentation of agglutinated cells on 5% albumin.[9,10] The agglutinated T lymphocyte depleted fraction can be dispersed by washing with D-galactose, the specific sugar inhibitor of SBA. Reisner et al. subsequently showed that this cell fraction could be used to reconstitute haematopoietic function in lethally irradiated H-2 incompatible mice, without GvHD.[8]

We record here the SBA lectin-binding characteristics of lymphoid and haematopoietic elements from human and cynomolgus monkey marrow.

Materials and Methods

Human Bone-marrow (BM) Cells

BM cells from healthy volunteers were obtained by aspiration from the iliac crest as previously described.[11]

Monkey BM Cells

BM cells from cynomolgus monkeys (*Macaca fesicularis*) were obtained either by aspiration from the femora, tibiae, and iliac crests of living animals or by flushing of marrow from the long bones of killed animals.

Isolation of BM Mononuclear Cells

Mononuclear cells were isolated from the heparinised marrow cell suspension by density gradient centrifugation over 'Ficoll-Hypaque' (Lymphoprep, Nygaard, Oslo, Norway) as previously described.[12]

Lectin

SBA was purchased from Vector Laboratories, Burlingame, California.

Separation of BM Mononuclear Cells by SBA

Ficoll-isolated BM mononuclear cells (2×10^8 cells/ml, 0·5 ml) were incubated in polystyrene tubes (17×100 mm) with SBA (0·5 ml, 2 mg/ml phosphate buffered saline [PBS]) for 5 min at room temperature. The cells were then gently layered on top of a solution of bovine serum albumin (5% w/v in PBS, 8 ml) in a 15 ml conical bottom plastic tube. After 10 min at room temperature the agglutinated cells sedimented while the unagglutinated cells remained at the interface with the bovine serum albumin solution. Top and bottom fractions were removed separately and transferred to 15 ml conical bottom plastic tubes. The cells were then suspended in 10 ml of D-galactose (0·2 mol/l) in PBS. After 10 min at room temperature the cells were collected by centrifugation (200 g, 5 min) and washed once more with D-galactose and then twice with PBS.

Fractionation of Human BM Cells by Sheep Red Blood Cells (SRBC) and SBA (fig. 1)

Immediately after aspiration, the bone-marrow cell suspension is mixed with 'Hetastarch' (McGaw Laboratories, Irvine, California,