Repetitive transcranial magnetic stimulation and electroconvulsive therapy: complementary or competitive therapeutic options in depression?

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Objective: *To examine issues pertaining to the potential clinical roles of repetitive transcranial magnetic stimulation (rTMS) and the relationship of these to the use of electroconvulsive therapy (ECT).*

Methods: *A review of studies was carried out comparing the use of rTMS and ECT, with consideration of issues relating to the populations in which rTMS may be applied.*

Results: *There have been a number of randomized comparisons of rTMS and ECT. There are limitations with these studies, but in general they indicate that in non-psychotic patients rTMS appears to have a similar rate of response to ECT and certainly seems to have meaningful clinical effects. There are a number of clinical subpopulations in whom rTMS, but not ECT, is suitable, and assessment of the effectiveness of TMS in these populations is required.*

Conclusions: *Repetitive TMS and ECT are likely to prove to be complementary clinical tools and the introduction of clinical programmes with rTMS will enhance patient options rather than replace the use of ECT.*

Key words: *depression, electroconvulsive therapy, repetitive transcranial magnetic stimulation.*

Repetitive transcranial magnetic stimulation (rTMS) is a new technique for the treatment of patients with depressive disorders that has been undergoing trials over the last 10 years. As a clinical technique, rTMS has now progressed to the point that clinical services are being developed in a number of western countries, including Australia.[1] In line with a recent revision of the Royal Australian and New Zealand College of Psychiatry (RANZCP) position statement on the use of rTMS, these programmes in Australia are required to be based around ongoing research. Despite the development of these clinical programmes, questions still remain about the clinical place for rTMS and the patient population in whom it should be applied. The aim of the present paper is to discuss some of these issues, particularly in light of an emerging literature comparing the effectiveness of rTMS with electroconvulsive therapy (ECT) in the treatment of severe depressive disorders.

CLINICAL TRIALS

The first stimulator capable of producing magnetic fields sufficient to produce the depolarization of nerve cells in the human brain was introduced in the mid 1980s, in the UK in Sheffield.[2] Stimulators capable of repetitive stimulation, the precursors of those currently used in

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clinical work, became available only in the early 1990s, and the first trials of rTMS in depression appeared some time later. These trials were initially small, with limited numbers of patients, and provided treatment for only short periods of time, usually 1–2 weeks.[3,4] However, these early trials clearly suggested that high-frequency stimulation, usually between 10 and 20 Hz, applied to the left dorsolateral prefrontal cortex (DLPFC), appeared to have antidepressant properties.

Since the mid-1990s a number of randomized double blind parallel trials of left DLPFC rTMS have been published. Several meta-analyses of the results of these trials have been conducted.[5–8] Despite differences in methods and concerns about effect sizes, all of these published meta-analyses indicate that high-frequency stimulation to the left DLPFC applied over a 2 week period has greater antidepressant effects than sham or placebo stimulation. This is reassuring, especially given that the majority of studies have been of treatment-resistant depression, included only a relatively small number of patients and provided treatment over a fixed, limited duration of 10 treatment sessions. It is highly likely with small trials in a very difficult and heterogenous patient group that some negative results will be found,[9] especially given differences in treatment and sham methods that can confound treatment effects.[1] In addition, the fixed short time of treatment is quite limited compared to all other antidepressant treatments, which act over a longer duration or, in the case of ECT, are provided in a flexible number of treatment sessions.

A second application of rTMS also appears to have significant antidepressant properties. In this paradigm, low-frequency stimulation, usually 1 Hz, is applied to the right DLPFC. In the initial study of this type, Klein *et al*. found that it was more effective than placebo in the treatment of a group of medication-responsive patients.[10] In a recent study by our group, low-frequency right-sided rTMS was compared to high-frequency left rTMS in a group of patients with severe treatment-resistant depression.[11] All the patients in that study had been previously treated with multiple courses of antidepressant medication (mean no. antidepressant trials: 5.9 ± 3.4). Both types of rTMS in that trial were found to be more effective then sham stimulation, and there was no difference in effectiveness between the two active treatment types. Clinically meaningful improvements in mood emerged in patients when they received 4 weeks of treatment, clearly suggesting that the 2 weeks of treatment used in many studies is suboptimal dosing of the treatment.

rTMS AND ECT

Over the last 4 years, a number of trials have been published in which rTMS has been directly compared to ECT in randomized controlled trials. In the first trial of this sort, Grunhaus *et al*. randomized 40 patients referred with depression for ECT, to either a course of rTMS or electroconvulsive therapy.[12] The rTMS was given for up to 20 days, with high-frequency stimulation applied to the left DLPFC; 1200 pulses were given per day at 90% of the resting motor threshold (RMT; 20 trains of 6 s duration). Relatively speaking, the dose of rTMS applied in that study was lower than in a number of more recent studies where rTMS has been applied at higher intensities, often 100% or 110% of RMT. Electroconvulsive therapy was applied initially with right unilateral placement, with a switch to bilateral stimulation in patients who failed to achieve a reduction in Hamilton Depression Rating Scores (HDRS) of >30%. The ECT dose was determined by the method of limits and given at 2.5-fold the seizure threshold. During the course of treatment, energy increases were used to maintain seizure duration of greater than 25 s. A minimum of six ECT treatments was applied per patient. In regards to efficacy, overall ECT had a more potent antidepressant effect then rTMS. This was particularly evident in patients with major depressive disorder and psychotic symptoms. However, in patients without any evidence of psychotic symptoms, there was no difference in response between the two groups.

In a second comparison of rTMS and ECT published in 2000, 32 patients who were experiencing a major depressive episode, and who had failed to responded to at least one course of medication, were randomly assigned to an unlimited number of treatments with RTMS or ECT.[13] The rTMS was applied to the left DLPFC at 100% of RMT. A total of 30–35 2 s trains at 20 Hz were applied per day, 5 days per week. Electroconvulsive therapy was provided 3 days a week to the non-dominant hemisphere at 100% of machine output (504 mC at stimulation width of 0.5 ms). The mean number of treatments in the ECT group was 6.2 ± 1.6, and in the rTMS group it was 12.2 ± 3.4. In the multivariate model used for analysis, there was an advantage of ECT over rTMS on all rating scores. However, there was no significant difference in the rate of remission between the two treatment arms, and the percentage improvement over the course of treatment on the HDRS was not significantly different. The significant advantage was found in the percentage in improvement on the Beck Depression Inventory.

The third study comparing ECT was published by Janicak *et al*. in 2002.[14] In that study, 25 patients with major depression deemed clinically appropriate for ECT were randomly allocated to rTMS (10–20 treatments at 10 Hz and 110% of RMT applied to the left DLPFC) or to bi-temporal ECT (4–12 treatments). A total of 22 patients completed treatment and were included in the study analysis. Patients in both treatment groups showed significant improvement in

depression scores, and there was no significant difference between the response in the two groups. Overall, there was 55% improvement in the rTMS group and 64% improvement in the ECT group. Six out of 13 rTMS patients achieved response criteria compared to five out of nine ECT patients; this difference was not significant.

Finally, the group in Israel led by Grunhaus who published the first randomized trial of ECT and rTMS have recently completed a second study.[15] In that study, 40 patients with non-psychotic major depression referred for ECT were randomized to rTMS or ECT. On this occasion, rTMS was again applied over the left DLPFC at 90% of the RMT, with 10 Hz trains applied for 4 weeks. The ECT was initially dosed by the method of limits and then at 2.5-fold the seizure threshold. Right unilateral non-dominant hemisphere electrode placement was used. Patients who did not achieve a 30% reduction in HDRS were again changed to bilateral electrode placement after six ECT treatments. The overall response rate for both groups in that study was 58%, 12 ECT patients and 11 rTMS patients meeting response criteria out of 20 patients in each group. There were no significant differences between response rates in the two treatment arms; 30% in each group met remission criteria (defined by a final HDRS score of <9).

In addition to these four randomized trials, one study has analysed relapse rates in patients who initially responded to a course of ECT or rTMS.[16] Forty-one subjects were carefully followed with monthly assessments over a 6 month period. They all received ongoing antidepressant medication but no further ECT or rTMS. There was no difference in relapse rates; four patients in each treatment group experienced a relapse. There was also no ongoing difference in depression (HDRS) or Global Assessment of Functioning (GAF) scores at 6 months. The same group has also investigated the response rates to ECT in patients who failed to respond to a course of rTMS.[17] In that study, 17 rTMS non-responders received ECT, with clinical response in seven (40%) of the sample. Both psychotic (4/12) and non-psychotic (3/5) patients responded. Finally, one study has investigated the value of substituting ECT with rTMS sessions in a randomized trial.[18] Eleven patients received ECT only (6 sessions, non-dominant right unilateral); 11 patients received two ECT sessions and eight rTMS sessions over 2 weeks. The substitution group had a similar antidepressant effect and reported fewer side-effects.

DISCUSSION

Although the results of the randomized comparisons of ECT and rTMS conducted to date are quite promising, there are limitations to the interpretation of the results of these studies. First, no trials have applied strict double-blind procedures because this would seemingly entail the unnecessary administration of a general anaesthetic in the rTMS treatment group, which seems difficult to justify. Second, the sample sizes included in each of these studies are relatively limited. This is of importance if we are interested in perhaps subtle differences in efficacy between two active treatments where studies would need to be of considerable size to have sufficient power. The question of whether rTMS is as efficacious as ECT is perhaps less crucial than the question of whether rTMS is effective in general. In the context of the 'high hurdle' set in comparison with ECT, it is reassuring that rTMS is consistently seen to have similar or only slightly less efficacy. The similarity in response rates between multiple trials also suggests a robustness of this effect. This is of note given that the 'dose' of rTMS used would currently be considered low or moderate in most of these trials, in regards to pulse number, intensity or treatment duration.

This raises an important question as to whether a comparison between ECT and rTMS is the correct way to be evaluating the appropriate use of rTMS. The appropriate methods for testing a new treatment are, obviously, dependent on the clinical use to which it is proposed that the technique is applied. There are a number of potential clinical applications for rTMS in the treatment of depression. The least likely application is that rTMS could be used as first-line treatment, in other words as an alternative to antidepressant medication (although a small group of patients may well choose rTMS over medication, if available). This group is likely to be quite limited by the commitment of regularly attending a clinic/hospital for treatment sessions, and there would be significant resource implications of the provision of rTMS compared to the prescription of medication. A second, more likely group of patients in whom rTMS may be offered, are patients who through significant medical comorbidity or through a state of pregnancy or lactation, are unsuitable for or unable to receive ECT for the treatment of severe depression. Although the current RANZCP guidelines specifically indicate that rTMS should not be used in patients who are pregnant, the highly localized effects of the magnetic field seem to compare favourably with the generalized effects of antidepressant medication and ECT in regards to theoretical risk to the unborn fetus. In regards to patients with medical comorbidity, because the risk of seizure induction with rTMS is very low and because there are no other obvious ways in which rTMS could exacerbate a comorbid medical condition (apart from neurological disease), rTMS would seem to be a preferable treatment to ECT. The latter has risks associated with repeated anaesthetic administration and seizure induction.

Third and possibility most importantly, there appears to be a large group of patients with treatment-resistant mood disorders in the community, who remain significantly disabled with depression, either

in spite of antidepressant medication treatment or because of inability to tolerate the side-effects of medication. Many of these patients are also unable to tolerate the side-effects of ECT or refuse to have ECT because of the associated stigma or fears about potential side-effects. The author's experience is that rTMS is frequently an attractive option for these patients who otherwise have few treatment alternatives. The final group of patients for whom rTMS may be of benefit are those patients traditionally referred for ECT treatment. This is a somewhat heterogeneous group comprising patients with severe treatment-resistant depression as well as patients with risks such as acute suicidal ideation and catatonia. It is unlikely that rTMS will, in its current form, replace ECT for the treatment of these patients because treatment courses with rTMS can take longer than ECT, and timely treatment response is obviously critically important in this patient population. However, there may well be a subgroup of patients traditionally referred for ECT, in particular those without psychotic symptoms or acute risks, for whom rTMS may be an attractive first option, prior to consideration of a course of ECT treatment.

It is obvious that in judging many of these potential indications, comparisons with ECT are of limited value. For example, for patients with resistant depression who are not likely to accept ECT treatment, a more valid comparison may be with a further trial of antidepressant medication or medication augmentation, because the clinical reality for these patients is that they often spend many months and years progressing through trials of almost every available medication type. Similarly, a more valid comparison for patients with medical comorbidity, pregnancy or lactation may be with the provision of a structured course of individual psychotherapy. However, it does seem likely that the widespread use of rTMS may reduce, but not replace, ECT, because some patients successfully treated with rTMS may otherwise have progressed to treatment with ECT. In addition, rTMS seems to have considerable potential as a maintenance treatment option, something that is possible with ECT but which is often difficult due to clinical and practical reasons. The use of maintenance rTMS should be assessed both after successful rTMS treatment but also after successful ECT.

On a broader scale and looking somewhat to the future, it is possible to envision a time when patients and psychiatrists are able to make a choice between a range of less or more invasive biological therapies for severe mood disorders. These will include treatments available today, such as antidepressant medication and ECT, but may also include rTMS, magnetic seizure therapy,[19] which is currently in the early stages of investigation for treatment-resistant mood disorders, as well as vagal nerve[20] and deep brain stimulation.[21] The choice of treatment may depend on the clinical circumstances, such as severity and acuity, as well as the acceptability of the treatment to the individual patient, who may progress from trials of less to more invasive therapies or 'jump' to more invasive options based upon clinical indicators. In this and the current context, rTMS should be considered as a complementary treatment to ECT rather than a competitor or a treatment tool that is likely to replace ECT in the therapeutic armamentarium of psychiatrists over coming years. Concerns that rTMS should or could replace ECT are best replaced by a focus on the development of increased therapeutic options for our patients, and criteria for selection of patients for each treatment based on predictors of response and side-effects.

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