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COMPARISON OF THERAPEUTIC EFFICACY OF ECT AND IMIPRAMINE : A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Efficacy studies comparing ECT and tricyclics in depression have had methodological limitations. This study compared ECT and imipramine (IMN) prescribed as the first line of treatment in major depression, Drug-naive, consenting, DSM-IV major depression patients (n=28), were randomized to receive either bilateral ECTs or IMN (225 mg/d) for four weeks. Severity of depression was scored at twice weekly intervals. Subjective side effects were scored at second and fourth week. Patients had significant reductions in depression scores over time but there were no differences between the two treatment groups. The rate of antidepressant response did not significantly differ between the two groups. ECT group had significantly fewer side effects. IMN offered therapeutic response comparable to ECT without compromising on the speed of antidepressant response, but caused more side effects.

Key words : Major depression, ECT, imipramine, therapeutic efficacy.

The antidepressant efficacy of both imipramine (IMN) and ECT is undisputed. But the most common indication for ECT in depression is nonresponse to pharmacotherapy (Weiner & Coffey,1988; APA, 1990). Current research on comparative efficacy of ECT and antidepressants has focused on drug-resistant cases (Dinan & Barry, 1989; Folkerts et al.,1997). Abrams (1997) noted that the case for therapeutic advantage of ECTs over antidepressant drugs rests primarily on three studies (Greenblatt et al.,1964; Shepherd,1965; Gangadhar et al.,1982). Rifkin (1988) and Abrams (1997) point to several methodological inadequacies viz., definition of depression, sample size, dose of the drugs and statistical analyses.

Nevertheless, one of the primary indications for ECT is when a rapid and definitive response is needed (APA, 1990; Abrams, 1997). The expected rapidity of response is hence important in choosing between antidepressant treatment options. The methodological problems in studies of the speed of antidepressant response were reviewed recently (Muller & Moller, 1998; Nobler et al.,1997). Among the important suggestions were, use of more frequent clinical rating, survival analysis statistics etc. This study examined the relative efficacy and speed of antidepressant response of ECT and IMN in major depressive disorder.

MATERIAL AND METHOD

Patients were recruited from the outpatient department of the National Institute of Mental Health and Neurosciences during a one year period on the following criteria: Major Depressive Disorder (DSM-IV), drug-naive status for the current episode of depression, a total score of more than 16 on the 17-item Hamilton's Rating

Scale for Depression (HRSD); age between 20 and 60 years and informed consent to participate in study. The patients were excluded if they had systemic or neurological illnesses, substance dependence, bipolar affective disorder, psychotic disorder, concurrent anticonvulsant drug usage or ECT in the past six months. A total of 152 major depressive disorder patients were screened. Diagnosis of the patients was independently confirmed using DSM-IV checklist by an experienced clinician (BNG). Thirty six patients met one or more exclusion criteria and 84 refused consent. The patients were kept drug free except for 'placebo-B complex' tablets in the first week. Two patients scored <8 on HRSD at the end of this week and were excluded. In none of the others (n=30) a reduction of >20% on HRSD occurred nor total HRSD became lesser than 17 before starting treatment. The study sample consisted of 30 patients. The patients were equally randomized to either ECT or IMN, treatment groups. One patients switched to mania during IMN treatment and was dropped. A randomly identified patient from the ECT group was omitted from the analysis (n=28). Patient groups were comparable on the pretreatment variables except illness severity (Table 1).

Modification of the ECT procedure was achieved using atropine 0.15 µg/kg, thiopentone 3 mg/kg and succinylcholine 1 mg/kg in that order intravenously. Intermittent positive pressure ventilation with 100% oxygen was provided till resumption of spontaneous and regular breathing. ECT was administered using a constant current, bidirectional brief pulse ECT device (NIVIQURE). The stimulus parameters of the device were as follows : amplitude (800 mA), pulse width (1.25 msec) and pulse frequency (125 pps). The total stimulus dose (mC) is adjusted by setting the stimulus train length (0.2-3.6s). Standard bifronto-temporal stimulus electrode position was used. The stimulus threshold was determined by the 'empirical titration procedure' during the first ECT for all the patients. This involved administering the stimulus from an initial dose of 30 mC upwards in steps. Initial two steps were of 15mC and subsequent steps were of 30 mC. The threshold stimulus dose was defined as the dose at which a EEG seizure of at least 25 seconds duration was obtained. Suprathreshold dose viz., 60 mC above threshold, was administered for subsequent ECTs. Both motor (right ankle/arm cuff) and EEG (F_3 & F_4 referenced to common mastoids) seizures were monitored. ECTs were administered twice weekly but reduced to once a week if HRSD scores were less than eight for a minimum of one week.

IMN was given orally at bed time in a dose of 225 mg/day, from the first day itself except in patients older than 50 years (n=4) for whom the dose was 150 mg/day. A trained psychiatrist (PM) who had randomized the patients was responsible for ensuring treatment and care during the trial period.

Assessments were independently carried out by a trained rater uninvolved with the treatment and without reference to the treatments. All assessments were done between 48 and 72 hours after the last ECT. The rater had no access to clinical records. Assessments included 17-item HRSD (Hamilton, 1967), six item subscale of HRSD (Bech & Rafaelson, 1986), DSM-IV melancholia checklist (APA, 1994), Montgomery-Asberg Rating Scale (MADRS); (Montgomery & Asberg, 1979), Clinical Global Impression (CGI); (Guy,1976) and Beck's depression inventory (BDI); (Beck et al.,1961). They were administered at pretreatment (baseline/day-0) and twice weekly thereafter for four weeks. Patients self-reported their improvement (no change to totally recovered) on a 100 mm Visual Analog Scale (VAS) twice weekly for four weeks after active treatment commenced. BDI items were read out and the patients responses were recorded on a video interview once a week (VBDI). The video records were edited for any disclosure of treatment given and were coded to mask their order in the treatment period. The two independent, trained researchers uninvolved in the study rated these video records. Side effects were rated at the end of two and four weeks using Columbia side effect check list (Sackeim et al., 1987).

Sociodemographic data, pre-treatment

illness severity and side effect check list scores were compared between the two groups using independent sample t-test. Total scores on HRSD, BDI and MADRS as well as VAS & CGI scores over time in the two groups were analysed using 2-way RMANOVA; pre-treatment total HRSD score was used as covariate. Time to remission of a symptom was defined by the number of days to the earliest assessment occasion on which it was rated zero. Between group differences in time to remission of individual symptoms (except lack of insight & loss of weight) of the HRSD were also examined using independent sample 't' test. The two treatment groups were also similarly compared on a measure of syndromic remission viz., total HRSD score <8. Time to remission was analyzed by Kaplan-Meier survival analysis. Significance (Alfa) was set at 5% level. Intraclass correlation was used to examine agreement between video BDI and corresponding clinical BDI scores at each of the weekly assessments.

RESULT

Rates of remission (HRSD<8) in ECT & imipramine group were 71% & 78% respectively. The mean scores & SD on the various instruments at each of the assessment occasions are provided in table 2.

On 2-way RMANOVA there was a significant occasion effect on total scores of HRSD ($F=35.1$; d.f.=208, 8; $p<0.001$), BDI ($F=16.2$; d.f.=208, 8; p0.001) and MADRS ($F=66$; d.f.=208, 8; $p<0.001$) as well as on VAS ($F=8.8$; d.f.=208, 8; $p<0.001$); CGI severity ($F=41.1$; d.f.=208, 8; $p<0.001$) & CGI improvement ($F=29.7$; d.f.=182, 7; $p<0.001$) scores. However, there was no significant group effect : HRSD ($F=0.07$; d.f.=26, 1; p<0.7), BDI ($F=0.13$; d.f.=26, 1; $p=0.6$), MADRS ($F=0.22$; d.f.=26, 1; $p=0.7$), VAS ($F=0.36$; d.f.=26, 1; p<0.6), CGI severity ($F=0$; d.f.=26, 1; $p=0.5$) & CGI improvement ($F=0.24$; d.f.=26, 1; $p=0.5$). There was a significant interaction effect: HRSD ($F=35.07$; d.f.=208, 8; $p<0.001$), BDI ($F=16.2$; d.f.=208, 8; $p<0.001$), MADRS ($F=16.2$; d.f.=208, 8; $p<0.001$), VAS ($F=21.4$; d.f.=182, 7; $p<0.001$), CGI severity ($F=41.1$; d.f.=208, 8; $p<0.001$) & CGI improvement ($F=29.7$; d.f.=182, 7; $p<0.001$). The six-item sub-scale of HRSD followed a similar pattern. There was a significant occasion effect ($F=23.4$; d.f.=208, 8; $p<0.001$) without group effect ($F=0.17$; d.f.=208, 8; $p=0.17$) and interaction effect ($F=1.3$; d.f.=208, 8; $p=0.3$).

All patients could not be interviewed on the video due to practical dificulties. Only 21 patients were interviewed on all four post-treatment weeks (of whom only 12 had interview at pre-treatment). This VBDI data of 21 patients was analyzed. There was a good correlation between the clinical (PS) and video assessment scores (NM); intraclass correlations (ICC) were 0.72, 0.86, 0.72, 0.81 on post treatment occasions 1,2,3 & 4 respectively. Ratings of one of the raters (NM) was used for the remaining analysis. On 2-way RMANOVA of the VBDI scores, there was no group effect ($F=0.2$; d.f.=16, 1; $p=0.7$), however there was a significant, occasion effect ($F=8.8$; d.f.=48,3; $p<0.001$) and interaction effect ($F=3.6$; d.f.=48, 3; $p=0.02$).

Patients with melancholic features (DSM-IV; n=21) were similarly analysed separately. There was a significant occasion effect with HRSD ($F=24.2$; d.f.=152, 8; $p<0.001$), BDI ($F=9.5$; d.f.=152, 8; $p<0.001$), MADRS ($F=41.7$; d.f.=152, 8; $p<0.001$), VAS ($F=13.2$; d.f.=133, 7; $p<0.001$), CGI severity ($F=27.2$; d.f.=152, 8; $p<0.001$) & CGI improvement ($F=27.2$; d.f.=133, 7; $p<0.001$). There was however no group effect: HRSD ($F=0.4$; d.f.=19, 1; $p=0.3$), BDI ($F=0.58$; d.f.=19, 1; $p=0.2$), MADRS ($F=0.57$; d.f.=19, 1; $p=0.2$), VAS ($F=0.02$; d.f.=19, 1; $p=0.7$), CGI severity ($F=0.25$; d.f.=19, 1; $p=0.4$) & CGI improvement ($F=0.25$; d.f.=19, 1; $p=0.2$). There was no interaction effect: HRSD ($F=1.6$; d.f.=152, 8; $p=0.2$), BDI ($F=2.6$; d.f.=152, 8; $p=0.06$), MADRS ($F=2.4$; d.f.=152, 8; $p=0.08$), VAS ($F=1.6$; d.f.=152, 8; $p=0.2$), CGI severity ($F=2.1$; d.f.=152, 8; $p=0.5$) and CGI improvement ($F=0.96$; d.f.=152, 8; $p=0.5$).

The side effect scores (Columbia scale) at week 2 and 4 in the ECT group (6.7±5.2; 4.9±5.5) were lower than the corresponding

TABLE 2
MEAN (SD) SCORES OF THE TWO GROUPS (ECT & IMN) ON DIFFERENT INSTRUMENTS (MEASURES) AT PRE- AND EIGHT POST-TREATMENT OCCASIONS

Days-Measure	Groups	Pre(0)	3	7	10	14	17	21	24	28
HRSD										
	ECT	28.2(3.9)	21.2(9.2)	15.6(11.2)	9.9(8.3)	7.0(7.4)	6.1(6.8)	5.8(6.2)	4.6(5.7)	3.8(5.0)
	IMN	24.7(4.9)	15.6(7.6)	11.4(8.7)	9.5(8.5)	7.5(7.4)	7.5(9.1)	8.2(8.4)	6.0(8.6)	5.8(8.5)
MADRS										
	ECT	46.8(6.4)	29.0(16.1)	21.7(15.9)	13.5(12.8)	10.2(12.2)	7.7(9.6)	8.2(10.6)	5.6(6.6)	4.2(5.8)
	IMN	39.5(6.0)	20.7(13.1)	15.5(14.1)	11.2(12.0)	8.8(11.3)	10.5(10.7)	10.7(12.4)	6.7(10.9)	8.2(12.4)
BDI										
	ECT	53.2(12.1)	37.3(18.0)	32.9(21.2)	22.4(20.7)	17.9(18.8)	15.1(16.3)	9.8(13.0)	8.4(11.1)	6.7(8.6)
	IMN	41.8(7.4)	29.7(18.2)	25.9(22.5)	16.9(18.1)	12.3(14.9)	18.4(21.0)	16.4(17.4)	13.1(18.0)	12.2(18.3)
VAS										
	ECT		27.9(32.3)	43.2(37.9)	64.7(32.3)	72.5(33.4)	76.5(27.3)	77.2(27.5)	86.1(21.8)	86.2(19.5)
	IMN		34.2(36.2)	51.3(43.3)	61.7(43.2)	59.8(38.3)	63.2(40.8)	72.2(36.8)	64.0(40.9)	72.4(37.7)
CGIs										
	ECT	5.7(0.7)	4.5(1.6)	3.5(1.8)	2.7(1.6)	2.1(1.3)	2.0(1.2)	2.1(1.2)	1.6(0.8)	1.5(0.6)
	IMN	5.4(0.5)	3.6(1.4)	3.2(1.8)	2.7(1.5)	2.2(1.4)	2.5(1.6)	2.2(1.6)	2.0(1.3)	1.9(1.4)
CGIi										
	ECT		2.7(0.9)	2.2(0.9)	1.7(0.7)	1.5(0.5)	1.5(0.5)	1.3(0.4)	1.2(0.5)	1.2(0.4)
	IMN		2.3(1.0)	2.1(1.0)	1.7(0.8)	1.6(0.7)	1.7(0.7)	1.7(0.9)	1.5(0.7)	1.3(0.7)
CGIe										
	ECT		2.0(0.8)	2.3(1.0)	2.9(1.0)	3.1(1.0)	3.0(0.9)	3.0(0.9)	3.2(0.9)	3.3(0.9)
	IMN		1.5(1.0)	1.8(1.5)	2.2(1.4)	2.3(1.3)	2.3(1.3)	2.1(1.3)	2.4(1.2)	2.4(1.2)

scores in the imipramine group (12.5±10.4; 9.4±9.5); ($p<0.05$ on both comparisons). On 2-way RMANOVA the CGI efficacy index scores rose over the 8 post-treatment occasions in both treatment groups ($F=2.5$; d.f.=182, 7; $p<0.05$) but mean scores of the CGI efficacy index were significantly higher in the ECT group ($F=4.2$; d.f.=26, 1; $p<0.05$).

Survival analysis (Kaplan Meier) showed that the time to remission did not show group differences: HRSD < 8 (Breslow statistic=0.03; d.f.=1; $p=0.8$) and CGI improvement ≤ 2 (Breslow statistic=2.1; d.f.=1; $p>0.5$). Further survival analysis of the number of days taken for 50% improvement in the HRSD scores also was not different between the two treatment groups (Breslow statistic=1.35; d.f.=1; $p=0.24$).

In the HRSD 'sleep items', only initial insomnia ($X^2=6.01$, $p<0.05$) & middle insomnia ($X^2=6.4$, $p<0.05$) scores dropped to zero earlier in the imipramine group than in the ECT group. Time to remission did not differ between the groups with respect to other individual symptoms including psychomotor retardation ($p>0.05$).

DISCUSSION

The high remission rates in both ECT and imipramine groups (71% & 78% respectively) could be because of several factors: 1) The patients were 'natural responders' for any somatic therapy as they were never treated for the current episode. In contrast, patients who failed to respond to medication were less likely to respond to subsequent ECTs (Prudic et al., 1989). 2) Majority of the patients were young and in their first episode of depression. With recurrent unipolar episodes and older age, treatment resistance increases (Avery & Lubrano, 1979). 3) Three quarters of patients had melancholic features indicating good prognosis on Newcastle prognostic scale (Carney et al., 1965). 4) Both treatments followed optimal standards: twice weekly bilateral ECTs & standard doses of imipramine. The response to ECT is as expected from earlier reports

(Greenblatt et al.,1964; Shepherd.1965; Jagadeesh et al.,1992; Gangadhar et al.,1993). The response to imipramine is however better than in other prospective controlled trials (Greenblatt et al., 1964; Shepherd, 1965).

Several randomized prospective trials had shown that ECT was more effective than tricyclic antidepressant drugs (Bruce et al.,1960; Robin & Harris, 1962; Fahy et al, 1963; Wilson et al, 1963; Greenblatt et al.,1964; Shepherd, 1965; Gangadhar et al.,1982). The same was not replicated in the present study. Out of these one study (Gangadhar et al.,1982) was the only strictly double blind study. This as well as the other studies had methodological pitfalls viz., heterogeneous patients population (Robin & Harris, 1962; Greenblatt et al.,1964) escalating doses of tricyclic antidepressant drug (Gangadhar et al.,1982), relatively low doses of imipramine (Wilson et al.,1963; Gangadhar et al.,1982) and unclear antidepressant status (Bruce et al.,1960; Fahy et al.,1963) and sine wave ECTs (Greenblatt et al.,1964; Shepherd, 1965; Gangadhar et al.,1982).

The study limited the role of 'placebo' response. Patients were recruited into the study only after confirming that they showed no placebo response to B-complex tablets during one week of observation in the ward. Placebo response was also less likely as three quarters of the patients had melancholic features. Also, separate analysis of patients with melancholic features did not detect between group differences. An early improvement of sleep and anxiety symptoms might give a spurious advantage to tricyclic antidepressant drug. Bech and Refaelson (1986) have identified six items of HRSD which represent the 'core depression' syndrome. The reduction of scores on this sub-scale can be regarded as a 'true antidepressant' effect. Comparison on this sub-scale too detected no group differences. The scores on MADRS which is more sensitive in detecting changes in depression also were not different in the two groups.

Although the study design did not follow the standard methodology of double blindedness, 'blind' ratings' was however ensured by the following: The rater did not have access to the clinical case records of the patient. Since the rating was carried out 48-72 hours after the last ECT session, the treatment identification by the rater was minimized. It is nevertheless recognized that the differential side effect profile (greater anticholinergic & sedative profile) of imipramine may have betrayed treatment identity and influenced HRSD ratings. VBDI was available at weekly intervals for most patients (n=21). The videos were edited to eliminate identification of both treatment status (rater blindedness was ensured) and occasion of assessment (order effect was excluded). It is arguable that differences between the groups were missed (Type II error) in the present study. Though the mean scores at baseline were higher in ECT group RMANOVA statistic took into account this difference. These methodological considerations were taken to confirm that the two treatments do not differ in either remission rate or time course of response.

The speed of remission with ECT was comparable to previous studies (Post et al.,1987; Rodger et al.,1994; Segman et al.,1995). These studies did not compare the speed of response of ECT to tricyclic antidepressant drug. Likewise, the speed of remission with imipramine is comparable to that reported by (Pollock et al., 1989; Malhotra & Santosh,1996) who was also used a relatively high initial antidepressant dose. The present study is the first prospective randomized comparison of ECT and imipramine with special reference to time to remission. The survival analysis found no difference in time to syndromic remission between ECT and imipramine. One of the reasons for this could have been that twice weekly ECTs in contrast to thrice weekly ECTs were administered. In prospective randomized designs the therapeutic advantages of thrice weekly ECTs over twice weekly ECTs has not been established unequivocally (McAllister et al.,1987; Gangadhar et al.,1993; Lerer et al.,1995). However there was an indication in one of the studies (Lerer et al.,1995) that speed of antidepressant response was faster in the thrice compared to twice weekly

ECTs. Contrastingly (Jagadeesh et al.,1992) suggested that the response to ECTs is time dependent and independent of the frequency of ECTs. In this context it is difficult to exclude the possibility that the lack of differences observed in this study are attributable to ECT frequency.

Yet another reason for a lack of advantage to ECT was that illness severity was lesser in the IMN than in the ECT group. In support to this argument, reported that a majority of tricyclic responders did so by the first week and responders were clinically less depressed relative to non-responders.

Do the two treatments differ with respect to individual symptom remission? As expected, the imipramine group achieved faster remission of sleep and psychic anxiety symptoms. Contrary to expectation (Browning & Cohen,1984; Hickey et al.,1996), however, psychomotor retardation responded at comparable speed in the two treatment groups. It is notable that ECT was superior on none of the symptoms.

Imipramine group had more adverse effects in comparison to ECT. This could be explained as tricyclics at high doses could produce greater anticholinergic side effects. The finding support previous observations that subjective side effect is greater with imipramine (Gangadhar et al.,1982). Interstingly, no patient developed a life threatening complication or intolerance necessitating discontinuation from the study despite high dose from the outset. Side effect assessments such as cardiac assessment and objective .memory scales were not administered in the study protocol. This is a limitation of this study. To compensate, a global measure of therapeutic and side effects interaction, CGI efficacy index was used. The efficacy index measures the side effect and therapeutic responses along two axes. The composite score of their interaction is obtained at each assessment point. Efficacy index was higher in the ECT group at all time points. This was expected as the side effect profile was worse in the imipramine group compared to ECT group and as no therapeutic differences between the two groups were noted. This brings forth the question : has ECT a place as a first line antidepressant treatment? The answer is yes as the therapeutic to adverse effect ratio was higher with ECT than IMN.

There is a need to assess the long term effects of these two modalities by means of short terms & long term follow up of the study cohort. The study could be extended to include bipolar depressives, psychotic depressive & elderly depressed individuals.

This study produced an unique challenge because it is difficult to recruit drug naive cases of the depression and subject them to receive ECTs as a first line of treatment given the established practice of antidepressant drug treatment every depressed patient would invariably obtain. The study findings must be viewed against this background as it provides an oppotunity to reassess an issue that ECT could be as effective and never inferior to a course of antidepressants in major depressive disorders and it is unwise not to administer ECT until the patient has not responded to antidepressant drugs.

In conclusion, first, both treatment groups showed a high remission rate although no treatment was superior to the other in therapeutic response. Second, time course of response was similar in both ECT and imipramine groups. Third, no symptom improved faster with ECT. Fourth, in view

TABLE 1
CLINICAL AND SOCIO-DEMOGRAPHIC DATA OF PATIENTS

Variables	ECT(n=14)	IMN(n=14)
Age(years)*	37.5(9.4)	42.4(12.1)
Sex(Male:Female)	7:7	10:4
Mamed:Never married	12:2	14:0
Years of Education*	5.1(6.3)	5.4(5.4)
Melancholia(Yes:No)	11:3	10:4
Episode duration(weeks)*	15.4(12.2)	20.3(11.9)
First:Recurrent episode	7:7	11:3
Family history(Yes:No)	2:12	3:11
Pretreatment HRSD	28.21(3.92)	24.71(4.96)
Pretreatment CGI severity	5.78(0.69)	5.42(0.51)

Cell contents refer to number of patients. In other cells* it refers to mean(SD). The two groups did not differ on any of the demographic and clinical variables except pretreatment HRSD(t=2.07, p=0.05)

of better efficacy of ECT compared to imipramine the role of ECT as the first line of management of depression merits further attention.

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