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Evaluation of donepezil and rivastigmine administration on the cognitive deficits induced by electroconvulsive therapy: a randomized, double-blind clinical trial

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A – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

Summary **Background.** Although several medical interventions have been used to reduce the cognitive side effects of electroconvulsive therapy (ECT), no specific drug has been yet identified to solve this problem.
Objectives. Because donepezil and rivastigmine are used to reduce the cognitive deficits in Alzheimer's patients, this study evaluated the effectiveness of these drugs on cognitive function in patients treated with ECT.
Material and methods. This randomized, double-blind clinical trial was performed on 60 patients with various mental disorders who were undergoing ECT as non-hospitalized patients or in the psychiatric ward of Golestan Hospital in Ahvaz, Iran. The subjects were divided into 3 groups of patients, receiving either donepezil, rivastigmine or a placebo. The Mini-Mental State Examination scores (MMSE) of the patients were evaluated before the initial ECT session, after the middle ECT session and after the final ECT session; the collected data were then analyzed using SPSS software version 22.
Results. The patients consisted of 25 females and 35 males at a mean age of 32.65 ± 8.81 years. The mean total number of ECT sessions was 7.41 ± 1.86 (p = 0.357). The mean of MMSE scores before the initial ECT session was 26.41 ± 1.35 in all patients, without a significant difference between the groups (p = 0.387). The mean of MMSE scores after the middle ECT session was 26.70 ± 1.41 for the donepezil group, 26.25 ± 1.29 for the rivastigmine group and 24.75 ± 2.07 for the placebo group; the MMSE scores of the placebo group were significantly lower (p = 0.003). Also, the mean of MMSE scores after the final ECT session was 26.75 ± 1.29 for the donepezil group, 26.40 ± 1.31 for the rivastigmine group and 24.50 ± 1.84 for the placebo group, which shows significantly lower scores in the placebo group (p < 0.001). The correlation between age and MMSE score after the ECT sessions was negatively correlated in the donepezil group.
Conclusions. The mean of MMSE scores in the placebo group was significantly lower than the donepezil and rivastigmine groups in the middle of the ECT and after the final ECT sessions.
Key words: electroconvulsive therapy, donepezil, rivastigmine.

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Background

Mental disorders are a major part of the medical concerns of today, and human health is being sought after the treatment of these disorders. For this reason, we need to use the best means and methods to manage these disorders [1–4]. Electroconvulsive therapy (ECT) is used as an effective and safe way to treat psychiatric illnesses, and it is usually done by applying two electrodes to the skull and causing generalized seizures through electrical stimulation [5]. Indications for ECT include unipolar depression, bipolar mood disorder, catatonia, schizophrenia and malignant neuroleptic syndrome. ECT is a safe, effective, low-risk and fast-acting method in cases of suicidal risk, severe psychotic disorder, drug-resistant cases, and conditions requiring a rapid response [6–11]. Headache and nausea are the most common side effects of ECT, which can be relieved with the use of analgesics and anti-nausea drugs. Other common complications include drowsiness, confusion and cognitive impairments following ECT [12]. ECT cognitive impairments have been reported as the most important limiting factors for using this method (with a prevalence of 12.4% for advanced memory) and they cause concern about patients' loss of memory. However, most patients return to their baseline cognitive status within 6 months of receiving ECT, though some of them report permanent memory problems [11–13].

Although numerous medical interventions have been undertaken to reduce the cognitive impairments following ECT, a specific treatment for improving memory has not yet been determined [14]. Acetylcholine is a neurotransmitter that plays a recognized role in memory and cognitive processes in humans, and some cognitive impairments improve with the use of factors that increase the effectiveness of the brain germline. It is anticipated that acetylcholinstrase inhibitors – drugs that are used as treatment for cognitive impairments in Alzheimer's patients [15] – may also be effective in reducing the subsequent complications of ECT.

In this regard, studies have been conducted on the efficacy of drugs such as rivastigmine and galantamine by increasing the amount of acetylcholine in the brain [16–17]. Donepezil has been approved by the FDA for the treatment of mild to moderate Alzheimer's disease, and it is a specific cholinesterase inhibitor. Donepezil, by raising the acetylcholine level, has

beneficial effects on cognitive impairments and daily living in Alzheimer's patients. In clinical trials, no significant adverse effects have been reported for the administration of donepezil in a large number of patients, a fact which is a major benefit of this drug [18]. Considering the use of donepezil to reduce cognitive impairments in patients with Alzheimer's disease, the efficacy of this drug on cognitive function in patients treated with ECT was investigated.

Rivastigmine is another acetylcholinesterase inhibitor in the nervous system which has beneficial effects on the cognitive impairments of Alzheimer's patients. Positive and significant results have been reported in several major meta-analysis studies on three cholinesterase inhibitors – including rivastigmine – on improving cognitive function in patients with mild, moderate or severe Alzheimer's disease [15–19] and no significant adverse effects or drug interactions have been reported [18].

Objectives

Because of the role of rivastigmine in reducing cognitive deficits in Alzheimer's patients, this study evaluated the effectiveness of this drug on cognitive function in patients treated with ECT.

Material and methods

Study design, setting, participants and variables

This study was performed as a double-blind, randomized clinical trial after enrollment in the Ethics Committee of the University on 60 outpatients and patients admitted to Golestan Hospital in Ahvaz, Iran who were candidates for ECT. The patients were randomly divided into 3 groups of 20 people in order to eliminate confounding factors.

Inclusion criteria. Patients aged 18–60, patients with various disorders – such as schizophrenia, schizoaffective disorder, bipolar mood disorder and major depressive disorder – whose disease was confirmed by a relevant psychiatrist in the study based on the DSM-IV-TR benchmarks and who underwent between 6–12 ECT sessions were considered, patients admitted to the psychiatric ward of Golestan Hospital, or non-admitted patients receiving ECT and resident in Ahvaz.

Exclusion criteria. The exclusion criteria consisted of patients with the following contraindications: epilepsy and other neurological disorders; hepatic failure; renal failure; cardiovascular disease; diabetes; dependence on or abuse of alcohol or drugs (with the exception of caffeine and nicotine) in the previous 6 months; pregnancy, breastfeeding, history of donepezil or rivastigmine use in the previous 3 months; history of drug allergy to donepezil and rivastigmine; patients receiving drugs such as phenytoin, carbamazepine, dexamethasone, rifampin, phenobarbital, paroxetine, ketoconazole or anticoagulants; chronic use of NSAIDs; delirium and dementia; a history of ECT in the previous 6 months or ECT-related cognitive problems; forced emergency ECT in the previous few hours; patients who did not undergo at least 6 ECT sessions for any reason; and patients with an MMSE score of < 24.

Randomization. The patients were randomly divided into 3 groups – 1, 2 and 3 – using a simple, randomized table.

Blinding. In this study, both the researchers and the patients were unaware of which of the three groups were receiving medication or the placebo. Both medications and the placebo were similar in shape, color and odor.

Design, protocol and data collection

In this study, the demographic data recorded were based on the patient's information and the records of the case, including age, sex, education and marital status. The patient was then evaluated by the MMSE test. The reliability of this test was calculated to be 0.78 with Cronbach's alpha and its cut-off point with 90% sensitivity and 84% specificity and equivalent to 21 calculated [20]. Patients received an average of 3 ECT sessions a week. The total number of ECT sessions was 6–12. During each session, 20 mg of propofol 1%, 20 mg of lidocaine 2%, 50 mg of succinylcholine and 0.05 mg atropine 1% was administered intravenously to induce anesthesia and muscle relaxation.

Drug intervention

48 hours before the ECT sessions began, the drug was administered. In order to maintain consistency between the three groups, the regulation of how to administer the drug was based on the group receiving more frequent medications.

Group number 1

A capsule containing 5 mg of donepezil (given in the same dosage throughout the study) was taken in the morning and a starch-containing capsule was taken as a placebo at night. The drug was administered until the final ECT session.

Group number 2

A capsule containing rivastigmine (1.5 mg twice daily, increasing over one week to 3 mg twice daily) was taken twice, in the morning and at night. The drug was administered until the final ECT session.

Group number 3

Placebo capsules were taken twice, in the morning and at night. The pills were administered until the final ECT session.

The MMSE test was repeated in patients from all three groups in the middle and the end of the ECT period.

Statistical analysis

The data were analyzed using SPSS 22; the significance level of the statistical tests was considered to be < 0.05. After analyzing and interpreting the results of the *t*-test, the sensitivity, specificity, accuracy and positive and negative predictive values were measured.

Results

Descriptive data

A total of 60 patients (25 female and 35 male) were enrolled in the study. Each group included 20 patients. The mean age of the patients was 32.65 ± 8.81 years, and there was no significant difference between the age of the groups ($p = 0.105$). The average number of ECT sessions in all of the patients was 7.41 ± 0.86, with no significant difference between the groups ($p = 0.357$).

Outcome data and main results

The mean of the patients' MMSE scores before the ECT sessions was 26.41 ± 1.35. There was no significant difference between the three groups ($p = 0.387$). The average of the MMSE scores in the middle of ECT sessions for all patients was 25.90 ± 1.81. This value in the placebo group was significantly lower than that of the other two groups ($p = 0.003$). The mean of the MMSE scores after the final ECT session was 25.88 ± 1.84. This value in the placebo group was significantly lower than that of the other two groups ($p < 0.001$) (Table 1, Figure 1).

The comparison of variables in the group receiving donepezil and rivastigmine showed that the mean age of the patients in the donepezil group was significantly higher than that of the rivastigmine group ($p = 0.03$), but no significant difference was observed in the other variables.

The analysis of variables in the donepezil and placebo groups showed that the mean of MMSE scores in the middle of the ECT sessions ($p = 0.001$) and MMSE scores after the final ECT session ($p < 0.001$) were significantly lower in the placebo group than those in the donepezil group.

The comparison of variables in the rivastigmine and placebo groups showed that the mean of MMSE scores in the middle of ECT sessions ($p = 0.009$) and MMSE scores after the final ECT session ($p = 0.001$) were significantly lower in the placebo group than those of the rivastigmine group.

Comparison of variables in the donepezil group

In the donepezil group, the variables were compared by gender and no statistically significant difference for age ($p = 0.259$), ECT number ($p = 0.83$), mean MMSE score before the initial ECT session ($p = 0.151$), mean MMSE score in the middle of ECT ($p = 0.604$) or mean MMSE score after the final ECT session ($p = 0.44$) were found. Moreover, the correlation between age and MMSE score after ECT was negatively correlated, so that with increasing age, MMSE score after ECT was lower.

The evaluation of MMSE score changes in the donepezil group at different times showed that the MMSE score did not change significantly in the middle of ECT compared to scores before the initial ECT session ($p = 1.0$), after the final ECT session compared to the middle of ECT ($p = 0.57$) or after the final ECT session compared to before the initial ECT session ($p = 0.78$) (Table 2).

Comparison of variables in the rivastigmine group

In the rivastigmine group, the variables were compared by gender and no statistical significant difference for age ($p = 0.51$) or ECT number ($p = 0.68$) were found, but the mean MMSE score before the initial ECT session ($p = 0.03$), the mean MMSE score in the middle of ECT ($p = 0.03$) and the mean MMSE score after the final ECT session ($p = 0.04$) were significantly lower in the male patients than that of the female patients.

The evaluation of MMSE score changes in the rivastigmine group at different times revealed that the MMSE scores did not change significantly in the middle of ECT compared to those before the initial ECT session ($p = 1.0$), after the final ECT session compared to the middle of ECT ($p = 0.08$) or after the final ECT session compared to those from before the initial ECT session ($p = 0.37$) (Table 3).

Comparison of variables in the placebo group

In the placebo group, the variables were compared by gender and no statistical significant difference for age ($p = 0.36$), ECT number ($p = 0.54$), mean MMSE score before the initial ECT session ($p = 0.41$) or mean MMSE score in the middle of ECT ($p = 0.83$) were found, but the mean MMSE score after the final ECT session ($p = 0.03$) was significantly lower in the female patients than in the male patients.

The evaluation of MMSE score changes in the placebo group at different times showed that the MMSE score in the middle of ECT compared to that from before the initial ECT session ($p < 0.001$) as well as the final ECT session compared to before the initial ECT session ($p < 0.001$) had significantly decreased, but no statistically significant difference was found between scores after the final ECT session and those from the middle of ECT ($p = 0.56$) (Table 4).

Finally, as previously stated, the mean MMSE scores from the middle of ECT and after the final ECT session in the placebo group were significantly lower than those in the donepezil and rivastigmine groups.

Table 1. Mean and SD for age, ECT number, MMSE score before the initial ECT session, MMSE score in the middle of ECT session and MMSE score after the final ECT session in the 3 groups

Variables	Donepezil (Group 1)		Rivastigmine (Group 2)		Placebo (Group 3)		*p*
	Mean	SD	Mean	SD	Mean	SD	
Age	35.0500	8.73875	29.3500	8.00838	33.5500	9.08136	0.105
Number of ECT sessions	7.7500	2.09950	7.3000	1.75019	7.2000	1.76516	0.357
MMSE score before the initial ECT session	26.7000	1.45458	26.2500	1.33278	26.3000	1.30182	0.387
MMSE score in the middle of ECT	26.7000	1.41793	26.2500	1.29269	24.7500	2.07428	0.003
MMSE score after the final ECT session	26.7500	1.29269	26.4000	1.31389	24.5000	2.01311	< 0.001

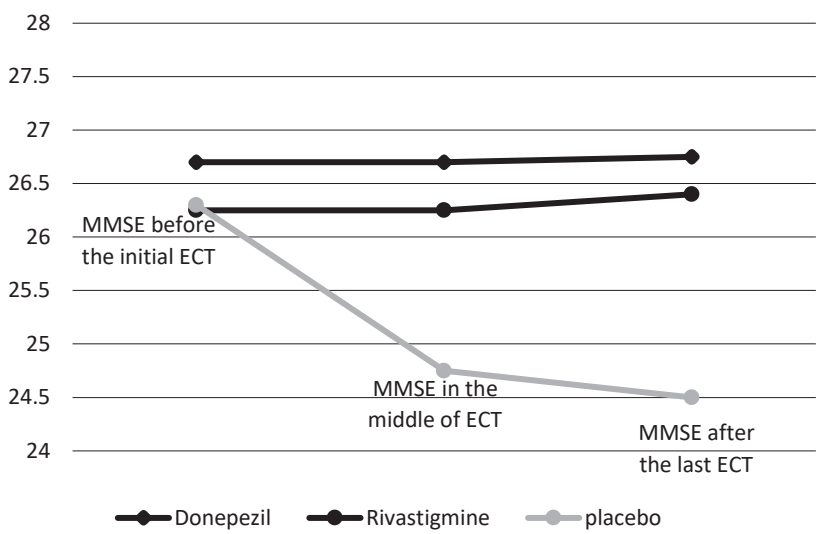

Figure 1. MMSE scores at different time-points in all 3 groups

Table 2. Evaluation of changes in MMSE score in the donepezil group at different time-points

Ratio	Time-point	MMSE score		*p*
		Mean	SD	
MMSE score in the middle of ECT compared to MMSE score before the initial ECT session	Before the initial ECT session	26.7000	1.45458	1.0
MMSE score after the final ECT session compared to MMSE score in the middle of ECT	In the middle of ECT	26.7000	1.41793	0.57
MMSE score after the final ECT session compared to MMSE score before the initial ECT session	After the final ECT session	26.7500	1.29269	0.78

Table 3. Evaluation of changes in MMSE score in the rivastigmine group at different time-points

Ratio	Time-point	MMSE score		*p*
		Mean	SD	
MMSE score in the middle of ECT compared to MMSE score before the initial ECT session	Before the initial ECT session	26.2500	1.33278	1.0
MMSE score after the final ECT session compared to MMSE score in the middle of ECT	In the middle of ECT	26.2500	1.29269	0.08
MMSE score after the final ECT session compared to MMSE score before the initial ECT session	After the final ECT session	26.4000	1.31389	0.37

Table 4. Evaluation of changes in MMSE score in the placebo group at different time-points

Ratio	Time-point	MMSE score		*p*
		Mean	SD	
MMSE score in the middle of ECT compared to MMSE score before the initial ECT session	Before the initial ECT session	26.3000	1.30182	< 0.001
MMSE score after the final ECT session compared to MMSE score in the middle of ECT	In the middle of ECT	24.7500	2.07428	0.56
MMSE score after the final ECT session compared to MMSE score before the initial ECT session	After the final ECT session	24.5000	2.01311	< 0.001

Discussion

The efficacy of donepezil and rivastigmine administration on the cognitive function of patients undergoing ECT and comparing the above groups with the placebo group showed the following results:

In evaluating the cognitive function of patients in the placebo group, although the mean of MMSE before the initial ECT did not show significant difference with the patients in the donepezil and rivastigmine groups, however, in the middle of the ECT session and after the final ECT session, the mean of MMSE in the placebo group compared to that of in the groups of donepezil and rivastigmine significantly decreased. This indicates a decrease in cognitive function in the placebo group following the administration of ECT as well as an effect cholinesterase inhibitors have in reducing the probable cognitive side effects of ECT. Considering the effective role of the cholinergic system on memory and cognition that has been demonstrated in some previous studies on humans and animals [21–22], drugs which influence this system can prevent and even improve cognitive function.

As, Martin et al. reported findings similar to those in this study about cognitive decline after ECT in a placebo group in the follow-up of 123 ECT patients. In their study, as in ours, the MMSE was used as a cognitive change measurement tool. They reported that the change in MMSE score predicted cognitive changes following ECT [23]. They found that cognitive changes, especially retrograde amnesia, occurred after 6 ECT sessions, but in the present study, the cognitive deficit began earlier in the placebo group, from the middle of the ECT course until the end of the final ECT session. In that study, the examination was performed 4 times (at baseline, after the third and sixth sessions and after the final ECT session), while the MMSE examination in this study was done 3 times (before, during and after ECT). Furthermore, the sample size was higher in that study and there was no intervention to reduce the cognitive side effects of the patients.

In the present study, the role and effects of drug interventions on cognitive function in both the donepezil and rivastigmine groups were studied. The comparison of mean MMSE scores in each group at different stages (before, during and after ECT) as well as in both groups showed that there was no significant difference. Meanwhile, compared to the placebo group, a significant decrease was observed in mean MMSE score in the middle of ECT and after the final ECT session, indicating a cognitive deficit in this group. Based on the results of this study, it seems that the use of two cholinesterase inhibitors, donepezil and rivastigmine, and reinforcement of the cholinergic system leads to a decrease in cognitive deficit, and — in the case of rivastigmine — even a slight improvement in cognitive function, although this finding was not statistically significant. Therefore, it is suggested that further studies should be performed on a larger number of patients and for a longer duration.

Prakash et al. compared the effect of donepezil and a placebo on 45 patients treated with ECT; they indicated a higher rate of improvement in the cognitive functions of the patients in the donepezil group. Prakash examined the cognitive deficits immediately after every ECT session and measured the recovery time for male patients with psychotic and mood disorders. The dose of donepezil was similar to that used in the present study, but the time intervals of the cognitive assessment and the questioner were different from the present study. Their results indicated an effective role of donepezil on the time of short-term cognitive improvement and alertness immediately after receiving ECT [24].

Also, Stryjer et al. investigated the preventative role of rivastigmine and a placebo in ECT-induced memory deficit in 30 patients with schizophrenic disorder. After the end of the ECT

course, the ADAS-Cog scale score was reduced in the rivastigmine group, indicating the efficacy of rivastigmine on memory deficits caused by ECT [25]. Although both the placebo and rivastigmine groups were similar in terms of cognitive function according to MMSE scale before the start of ECT, after the end of ECT sessions cognitive function in the placebo group was significantly lower than in the rivastigmine group and there was no change in the rivastigmine group. This study provides further support for the cholinergic system's involvement in ECT-induced cognitive impairment. The significant difference between the present work and Stryjer's study is that the patients were all suffering from schizophrenia in the latter, which included basic impairments in cognitive processes due to the nature of this disorder. Also, the population under study and the maximum dose of rivastigmine (4.5 mg) were less than those of the current study.

In the study of Mattews et al., the use of galantamine in the middle of the ECT period led to a reduction in ECT-induced cognitive impairment and played a protective role in maintaining new learning. In that study, the patients had different disorders such as psychotic and mood disorders. The number of ECT sessions was not determined, and the average age of participants in that study was higher than in the present study. The assessment tool was also a modified MMSE (3MSE) and neuropsychological status assessment tests [17].

Limitations of the study

This research study was carried out in a single center and the number of patients was limited because of this problem.

Conclusions

The results of the present study and its comparison with other similar studies indicate a better cognitive function at the end of ECT in patients who receive cholinesterase inhibitors. The side effects of the drugs were not reported, which indicate a good tolerance of this category of drugs. Also, in the donepezil group, the mean MMSE score decreased with age, although the cognitive function of these patients did not change during the review period or at the evaluation intervals. Hence, further evaluation in these areas is suggested in future studies.

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