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The impact of melatonin on the alleviation of cognitive impairment during electroconvulsive therapy: A double-blind controlled trial

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ABSTRACT

Background: The purpose of this study was to assess the efficacy and safety of melatonin in the prevention of cognitive impairments during ECT treatment.
Methods: Forty patients diagnosed with a major depressive disorder, for which ECT was indicated as a treatment for their current episode, were randomly allocated to either the melatonin (3 mg/day) group or the placebo group. The patients received melatonin or the placebo for the whole period of the ECT treatment, starting the day before ECT and continuing until the sixth session of ECT. The Modified Mental State Examination (MMSE) and item 3 MMSE were used for the assessment of cognition. Objective measures of cognitive functioning were performed pre-ECT and post-ECT.
Results: In both the MMSE score and item 3 MMSE, the melatonin group scored significantly higher at the end of the ECT sessions than the control group ($P < 0.02$, $P = 0.001$, respectively). None of the patients discontinued the melatonin or placebo due to side effects and there were no severe adverse drug reactions.
Conclusion: Although our data support the hypothesis that melatonin may reduce cognitive impairment following ECT, we believed that the findings provide an additional benchmark for further studies involving more patients.

1. Introduction

Electroconvulsive therapy (ECT) is the most effective acute treatment for severe depression, but widely held concerns regarding memory impairment may limit its use (Kirov et al., 2016). Most patients report some adverse cognitive effects during and after a course of ECT. A systematic review of four observational studies (597 patients treated with ECT) found that the proportion of patients who reported any memory loss ranged from 51 to 79 percent (Arevalo-Rodriguez, Smailagic et al., 2015). The incidence depends upon electrode placement, stimulus type and dose, anesthesia, and the patient's pretreatment cognitive status (Matthews et al., 2013). Despite the large amount of literature on the neurobiology of therapeutic mechanisms of ECT, very little is known regarding the neurobiological underpinnings of its cognitive effects (Nobler & Sackeim, 2008). The neuroprotective effects of a number of pharmacological agents have been studied in previous animal and clinical studies. Most previous studies have evaluated anticholinesterase drugs to prevent or alleviate cognitive abnormality induced by ECT (Pigot, Andrade, & Loo, 2008). Other than cholinergic agents, Cyclo-Oxygenase 2 inhibitors, calcium channel blockers, nootropic agents, glucocorticoids and N-methyl-D-aspartate receptor antagonists have been tried for the alleviation of ECT-induced cognitive disorders (Abbasinazari, Adib-Eshgh et al., 2015). However, as yet, no pharmacological agent has been proven to consistently attenuate ECT-induced memory impairment.

Melatonin (N-acetyl-5-methoxytryptamine) is the main hormone synthesized by the pineal gland and is controlled by the suprachiasmatic nucleus(Waller et al., 2016). Melatonin and melatoninergic drugs have hypnotic effects mediated through two main receptors, namely MT1 and MT2 receptors, which act on the hypothalamic sleep switch. A beneficial effect of melatonin in neurodegenerative diseases has been reported in several studies (Carpentieri, D & az De Barboza, Areco, Peralta López, & Tolosa De Talamoni, 2012). A slight improvement in cognitive function was observed when melatonin was given to Alzhei-

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mer's Disease (AD) patients (Asayama et al., 2003). In addition, a retrospective study showed that melatonin treatment improved cognitive performance and sleep quality in patients with mild cognitive impairment (Furuya et al., 2012). Several neurodegenerative diseases, such as AD and Parkinson's Disease (PD) are characterized by more irregular circadian rhythms and lower melatonin content than in age-matched controls (Waller et al., 2016). Also, patients with AD have a reduction in melatonin concentration, both in blood and cerebrospinal fluid, which is even present in early stages (Wu & Swaab, 2005). The aim of the present study was to evaluate the potential use of melatonin in the alleviation or prevention of cognition impairment in patients undergoing ECT. We were also interested in exploring the safety and tolerability of melatonin in patients receiving ECT.

2. Methods

2.1. Study design

This study was designed as a randomized, double-blind trial. The study setting was the psychiatry department of Taleghani Hospital, affiliated with Shahid Beheshti University of Medical Sciences, Tehran, Iran. This study was carried out in accordance with the most recent Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013). The study was reviewed and approved by the ethical committee of Shahid Beheshti University of Medical Sciences. Also, all the subjects signed consent forms after the study procedures were thoroughly explained. Trial was registered in Iranian clinical trial registry site with number IRCT201510324793N31.The criteria for inclusion in the study were a comprehensive psychiatric evaluation in which the patient met the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V) criteria for a major depressive disorder, for which ECT was indicated as a treatment for their current episode. All subjects received a comprehensive psychiatric evaluation and were given a diagnosis based on DSM-V criteria. Criteria for exclusion from the study were a history of schizophrenia, schizoaffective disorder, bipolar disorder I or II, or rapid cycling bipolar disorder. Patients with heart conduction dysfunction, bradyarrhythmia, liver or kidney disorders, or opioid dependency were also excluded from the study. Furthermore, medications such as cholinergic agents, COX-2 inhibitors, calcium channel blockers, nootropic agents, glucocorticoids or memantine were avoided before or during the study.

2.2. ECT protocols

ECT was performed using a square-wave, brief pulse, constant current device (MECTA 5000). The patients received melatonin or the placebo for the whole period of the ECT treatment, starting the day before ECT and continuing until the sixth session of ECT. As ECT was performed every other day in all participants, the duration between the first ECT and the sixth ECT was 12 days. Anaesthetic agents included propofol (AstraZeneca, England) at an average dose of 0.5–1 mg/kg, succinylcholine (Caspain, Iran) 20 mg and atropine (Alborzdaru, Iran) 0.5 mg. The placement of electrodes was right unilateral, following the standard D'Eliaplacement. For all subsequent treatments, stimulus intensity was maintained at 50–100% above the initial seizure threshold. A custom-modified MECTASR-1 was used for stimulus delivery. Vital signs were examined prior to and during the 5-min period following seizure termination. The stimulus frequency was 90 Hz and the stimulus duration ranged from 1 to 4 s. Seizure monitoring was performed using a two-lead electroencephalogram of the right and left hemispheres, as well as visual monitoring of residual motor convulsive activity.

2.3. Measures

The participants, who were admitted to receive ECT, were divided in either a melatonin or placebo group. We utilized an online statistical computing web program to randomize participant placement (www.graphpad.com/quickcalcs/randomize1.cfm). A student who was not involved in the volunteer recruitment classified patients into the melatonin or placebo group by using the mentioned web program. Opaque boxes were filled with either placebo or melatonin tablets and sealed and numbered to correspond to the web program generated sequence. All the patients had received ECT between 10–12 AM and the pateints were asked to take memantine or placebo at around 8–9 P.M each night.

Demographic and hemodynamic parameters of eligible patients had been determined before enrolling on the study. Then, the participants were given 3 mg/day of melatonin or a placebo, beginning the day before the first session of ECT until the sixth session of ECT. A test to measure cognitive functioning, namely the Modified Mental State Examination (MMSE), was administered to patients both pre-ECT and post-ECT. Pre-ECT ratings were measured 24 h before the first ECT course, and post-ECT ratings were measured 24 h after the last ECT course. MMSE is well-known and the most often used short screening tool for providing an overall measure of cognitive impairment in clinical, research and community settings. The MMSE consists of 12 items and has a highest score of 30, with the score inversely related to cognitive abnormality. Traditionally, a 23/24 cut-off has been used to select patients with suspected cognitive impairment (Arevalo-Rodriguez, Smailagic et al., 2015). Also, item 3 in the MMSE questionnaire on recent memory was used to assess the 2 groups. In item 3 of the MMSE, the examiner names three unrelated objects clearly and slowly, then asks the patient to repeat all three. The patient's answer is used for scoring. The examiner repeats the names of the three objects until the patient learns all of them, if possible. The highest score is 3 and the lowest is 0 (Abbasinazari, Adib-Eshgh et al., 2015).

2.4. Statistical analysis

Data were analysed using the Statistical Package for the Social Sciences version 20 (SPSS-20), and P values less than 0.05 were considered statistically significant. Categorical data were analysed with chi-square statistics. The continuous data obtained in this study were analysed using a *t*-test or Mann– Whitney *U* test.

3. Results

Forty eligible patients (undergoing ECT therapy) completed the study. The mean age of the participants was 35.4 ± 12.9 and 52.5% of them was female. The flow of the participants through the study is shown in Fig. 1. Table 1 provides clinical variables for the melatonin and placebo groups. No significant group differences were noted for the initial level of cognitive functioning (MMSE and item 3 MMSE). There was no significant group difference in age between the two groups ($p = 0.450$). Also, the two groups had similar gender distributions; the melatonin group was 55% male and the placebo group was 40% male ($p = 0.527$). Also, no significant differences were noted for education level, domicile and duration of illness between the melatonin and placebo groups.

Table 2 provides the means for a number of ECT relevant variables. As Table 2 shows, there were no significant differences between the groups as regards systolic and diastolic blood pressure, heart rate and seizure time.

Fig. 2 summarizes the mean MMSE scores for the melatonin and placebo groups at the baseline and just end of the sixth course of ECT. Although the MMSE score was lower in the melatonin group compared with the placebo group at the baseline ($p = 0.049$), it had been raised significantly in the melatonin group compared with the placebo group after the sixth section of ECT ($p < 0.001$). Also, the melatonin group scored higher at the end of the sixth ECT session for MMSE and this was statistically significant ($P < 0.001$). In the placebo group, the MMSE

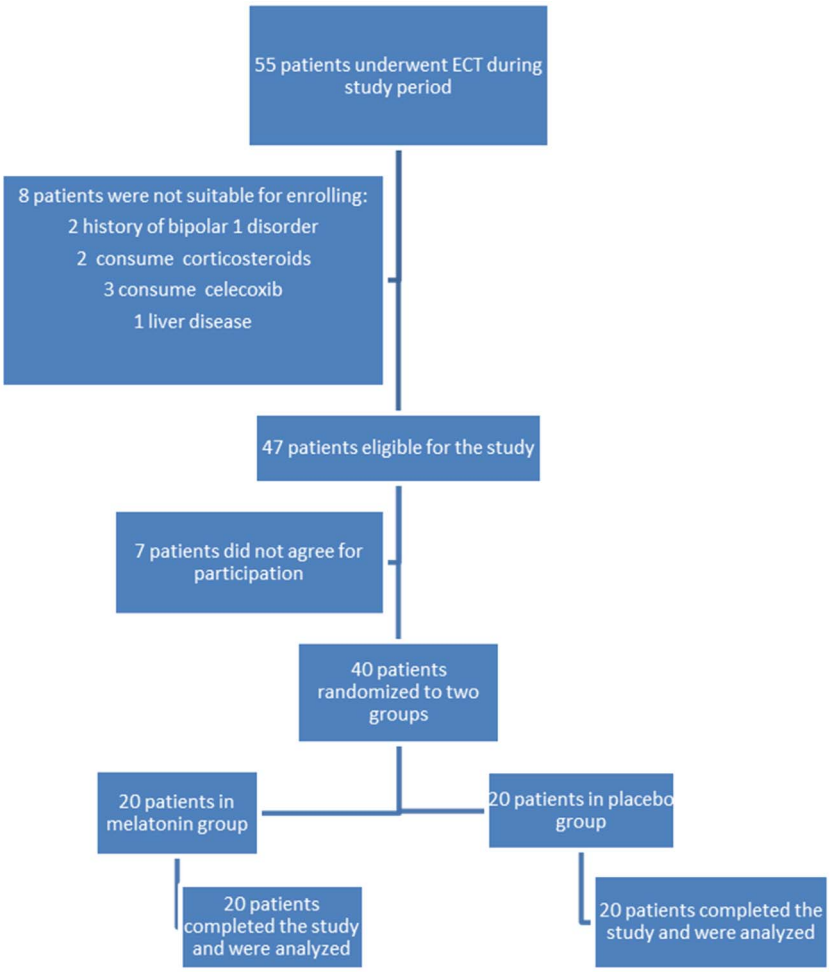

Fig. 1. Flow of the study.

Table 1
Demographic and cognitive parameter score of studied patients at baseline.[a]

Variable	Study Group		P Value
	Melatonin (N = 20)	Placebo (N = 20)	
Age, year	33.85 ± 12.7	37.0 ± 13.4	0.450
Gender, N (%)			0.527
Male	11 (55)	8 (40)	
Female	9 (45)	12 (60)	
Marital Status, N (%)			0.341
Single	11 (55)	7 (35)	
Married	9 (45)	13 (65)	
Educational level, N (%)			0.236
1	6 (30)	4 (20)	
2	9 (45)	9 (45)	
3	0 (0)	3(15)	
4	3 (15)	4 (20)	
5	2 (10)	0 (0)	
Past psychiatric duration, month	8.2 ± 2.7	7.75 ± 2.6	0.537
MMSE baseline score	26.85 ± 2.25	28.15 ± 1.09	0.049
Item 3 MMSE baseline score	2.5 ± 0.53	2.45 ± 0.51	0.755

[a] Abbreviation; Mini–Mental State Examination (MMSE).

scores decreased after ECT significantly ($P < 0.001$).

Fig. 3 summarizes the mean item 3 MMSE scores for the melatonin and placebo groups at the baseline and just end of the sixth course of ECT. Item 3 score was not different between the two groups at the baseline ($p = 0.755$). Also, there was no difference before and after the ECT course in each group ($p = 0.102$ in melatonin and $p = 0.058$ in placebo group). However, after the sixth ECT therapy, the melatonin group had an increased score in item 3 MMSE compared with the placebo group, which was significant ($p = 0.02$).

Table 2
Comparing seizure time (sec), systolic and diastolic blood pressure (mmHg), post-ECT heart-rate (/min), and past-psychiatric duration (month) between the two groups.

Variable	Study Group		P Value
	Melatonin (N = 20)	Placebo (N = 20)	
Seizure time, Sec	25.96 ± 3.39	24.48 ± 3.71	0.194
Systolic blood pressure, mmHg	115.5 ± 8.9	115.5 ± 8.3	0.778
Diastolic blood pressure, mmHg	74.5 ± 7.6	75.5 ± 7.6	0.586
Post ECT Heart rate,/min	78.05 ± 8.7	77.7 ± 6.6	0.886

During the study, all of the patients tolerated either melatonin or the placebo and no patients dropped out because of adverse side effects from those medications.

4. Discussion

ECT is considered a safe and effective treatment for patients with major depressive disorder. The main side effects of ECT are in the realm of cognition, in particular memory impairment (Arts et al., 2006). The

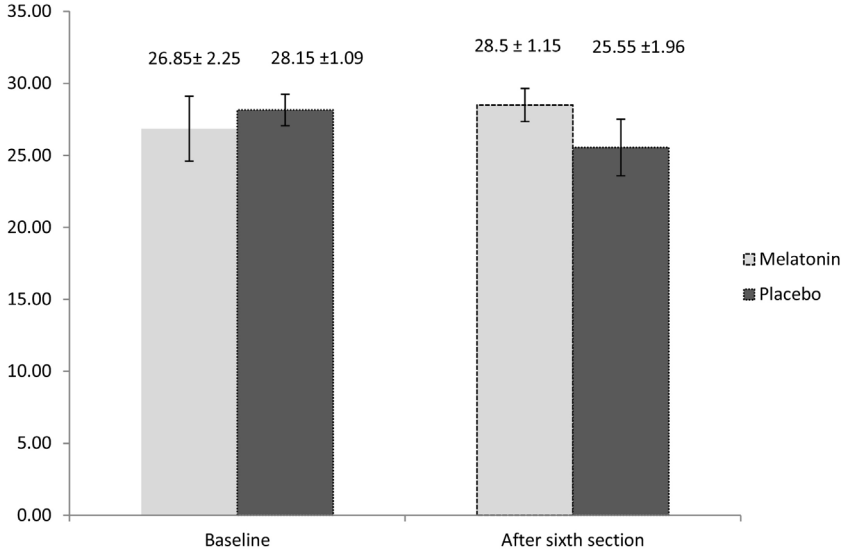

Fig. 2. Comparing baseline and after 6^{thECT} session MMSE score (± SD) between the two groups.

incidence of memory loss depends upon electrode placement, stimulus type and dose, anesthesia, pulse width, duration of seizures and the patient's pre-treatment cognitive status (Matthews et al., 2013). In our study, both groups were equal in number with no significant differences in the parameters listed above.

Melatonin has been shown some efficacy in relieving memory disorders in Alzheimer's patients (Simon, Frechilla, & del Rio, 2010). Deposition of Amyloid β-protein(Aβprotein), oxidative stress, and their neurotoxic effects are suggested as the major contributing factors for the pathogenesis of AD. Intra-mitochondrial accumulation of Aβ protein, inhibition of respiratory complexes, increased electron leakage, decreased oxygen consumption, and decline of adenosine-5-triphosphate (ATP) levels caused by increased oxidative stress are the major reasons for the neuronal cell death seen in AD. As melatonin has significant antioxidant properties, it can be of therapeutic value in arresting the progression of AD (Simon et al., 2010; Christen, 2000). The molecular mechanisms contributing to ECT induced cognitive deficits are poorly understood and there is not any gold standard for prevention or alleviation for ECT induced cognition disorders. Although AD develops during several years, in previous studies anti AD medications such as memantine, galantamine and donepezil have been tried for prevention of ECT induced cognition and in some trials advantage of these medications have been reported (Pigot et al., 2008). Our hypothesis for this study was that melatonin is effective in alleviating cognition disorders induced by ECT. We have used MMSE as an indicator of cognition impairment before and after ECT. It is the most applied test for the assessment of ECT-induced cognitive disorders after the prescription of a medication in the ECT setting(Pigot et al., 2008; Nehra et al., 2007). MMSE scores significantly decreased in the placebo group at the end of the study ($P < 0.001$). However, in the melatonin group, MMSE increased significantly after the end of the study ($p < 0.001$). Also, there was a significant difference between the two groups after undergoing ECT ($P < 0.001$). Considering MMSE, the results of this study provide evidence that melatonin may protect against cognitive deficits following ECT.

Item 3 of the MMSE (related to recent memory) appears to be more reliable for the interpretation of cognitive impairment versus total MMSE. Thus, we evaluated it separately in addition to total MMSE. Although there is no significant difference between item 3 MMSE before and after ECT in both groups, our study showed an increase in item 3 score in melatonin and a decrease in item 3 score in the placebo group. Statistical analysis showed that there is a significant difference between

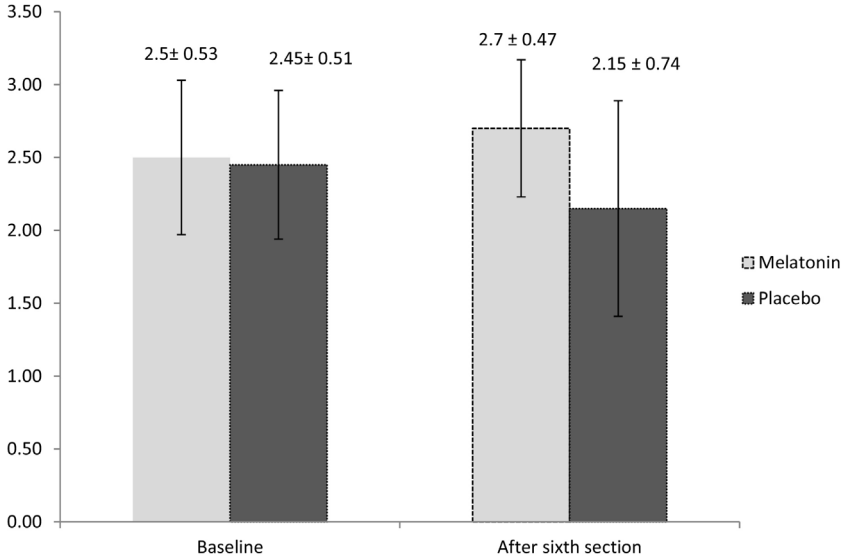

Fig. 3. Comparing baseline and after 6^{thECT} session item 3 MMSE score (± SD) between the two groups.

an item 3 score in melatonin and the placebo group after ECT ($p = 0.02$). Therefore, regarding item 3 MMSE, melatonin could be effective in the alleviation of ECT-induced cognitive disorder.

In agreement with previous studies regarding the role of melatonin in the enhancement of cognition (Asayama et al., 2003), we have found a positive effect of melatonin in the alleviation of post ECT-induced cognitive disorder. This is the first clinical trial to study the effect of melatonin on ECT therapy-induced cognitive impairment. We have noticed that melatonin 3 mg/d tolerated well in this setting. We were limited in the sample size of the study and the use of higher doses. We believed that the findings provide an additional benchmark for further studies involving more patients.

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