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The effect of liothyronine supplementation on electroconvulsive therapy-induced cognitive impairment in patients with mood disorders: a clinical trial

Pooya Hazegh [1 *], **Fatemeh Sadat Ghoreishi** [1], **Fatemeh Assarian** [1], **Amir Ghaderi** [2 *]

[1] Department of Psychiatry, School of Medicine, Kashan University of Medical Science, Kashan, Iran
[2] Department of Addiction Studies, School of Medicine AND Clinical Research Development Unit, Matini/Kargarnejad Hospital, Kashan University of Medical Sciences, Kashan, Iran

[*] **Corresponding authors:**
Amir Ghaderi, Department of Addiction Studies, School of Medicine AND Clinical Research Development Unit, Matini/Kargarnejad Hospital, Kashan University of Medical Sciences, Kashan, Iran.
E-mail: gaderiam@yahoo.com
Pooya Hazegh, Department of Psychiatry, School of Medicine, Kashan University of Medical Science, Kashan, Iran.
E-mail: pooyahazegh@gmail.com

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Abstract

Objectives: This study aimed to assess the effects of Liothyronine supplementation on memory performance in patients diagnosed with mood disorders (major depressive or bipolar disorder).

Methods: This double-blind controlled clinical trial was conducted on patients with major depression and bipolar disorder. The participants were randomly assigned to either the intervention group receiving Liothyronine or the placebo group, with 33 patients in each group, for a duration of one month. Memory performance was assessed before the first, fourth, and final Electroconvulsive therapy (ECT) sessions, as well as one month after the last session using the Wechsler Memory Scale-Revised (WMS-R). Data analysis was performed using independent-samples Chi-square test and the Greenhouse-Geisser correction factor.

Results: Liothyronine significantly enhanced communicative learning and visual memory in patients with major depression and bipolar disorder one month after the final ECT session. Additionally, a positive effect of Liothyronine on immediate recall was observed before the last ECT session.

Conclusion: Liothyronine supplementation improves ECT-induced cognitive impairment in patients with major depression and bipolar disorder. Further research is necessary to fully comprehend the potential of Liothyronine as an adjunctive treatment for major depression and bipolar disorder.

Keywords: Liothyronine, Electroconvulsive Therapy, Memory, Depressive Disorder, Bipolar Disorder.

Introduction

Mental illnesses affect an estimated 900 million individuals worldwide, representing 19% of the global population. The prevalence of mental disorders in Iran ranges from 21% to 34.2%, attributed to factors such as population growth, economic challenges, and social issues like family breakdown.[1] Electroconvulsive therapy (ECT) remains a highly effective treatment for major depressive disorder and critical psychiatric conditions, offering rapid relief without causing cerebral damage under general anesthesia.[2-4] ECT is considered safe with no absolute contraindications, even during pregnancy.[3,5] However, a significant drawback of ECT is the cognitive impairment it can induce,[6] with retrospective amnesia being a particularly severe complication.[2,7] Up to 75% of patients identify amnesia as the most distressing ECT-related issue,[3] and persistent amnesia affects 29% to 55% of patients, though its underlying causes remain debated.[8,9]

Given the substantial impact of ECT-induced cognitive impairments, various studies have explored strategies to prevent or alleviate these effects. Previous research has suggested the potential efficacy of interventions such as

donepezil,[10-12] rivastigmine,[6] galantamine,[13] naloxone,[9,14] physostigmine,[15] glucocorticoid antagonist CORT 108997,[16] dexamethasone,[17] and memoral herbal supplements in memory retrieval.[18] However, findings regarding piracetam's effectiveness remain inconclusive.[10,19,20]

Thyroid hormones play a crucial role in brain function, with thyroid disorders linked to emotional and cognitive symptoms and implicated in dementia development.[21,22] Studies have highlighted the relationship between cognition and thyroid function,[23] prompting investigations into the use of thyroid hormones, particularly liothyronine, to mitigate cognitive complications post-ECT.[2] Previous research has demonstrated the protective effects of liothyronine against electroshock-induced amnesia.[2,24,25] A systematic review by Verdijk et al.,[26] underscored the potential of liothyronine and Memantine in reducing ECT-related cognitive side effects, warranting further exploration. Notably, liothyronine was found to prevent ECT-induced amnesia in a study comparing its efficacy with piracetam and placebo.[18] In another study comparing liothyronine with vitamin B12 in depressed patients undergoing ECT, liothyronine reduced memory loss post-treatment, though its impact on specific Wechsler memory subscales like visual memory was not significant. Additional studies have highlighted liothyronine's effectiveness in preventing ECT-induced amnesia and enhancing patients' mood.[27,28]

Objectives

Given the significance of this topic, and the continued use of bilateral ECT in Iran, we aimed to investigate the effects of liothyronine in mitigating ECT-induced cognitive impairments.

Methods

This study was registered on the Iranian website for clinical trials (http://www.irct.ir: IRCT2015081823673N1) and conducted as a randomized, double-blind, placebo-controlled clinical trial involving 66 patients diagnosed with mood disorders (major depressive or bipolar mood disorder), aged 18 to 45 years, who were referred to Kargarnezhad Psychiatry Hospital in Kashan, Iran.

Inclusion criteria comprised patients aged 18 to 45 years with a diagnosis of a mood disorder (major depressive disorder or bipolar mood disorder) based on DSM-IV-TR criteria, absence of liothyronine sensitivity, and a negative pregnancy test before treatment initiation. Exclusion criteria included unstable cardiovascular disease, history of myocardial infarction within the past 3 months, current unstable angina, untreated endocrine disorders, uncontrolled hypertension, recent cerebral infarct or hemorrhage within the past month, untreated or bleeding vascular aneurysm, severe respiratory disorders, heart valvular disorders, brain structural anomalies causing increased intracranial pressure, addiction (excluding smoking) during the study period, ECT treatment within the past 6 months, mental retardation, delirium, dementia or other amnestic disorders, occurrence of ECT-induced delirium during the study, and lithium administration during the study.

Patients diagnosed with a mood disorder at Kargarnezhad Psychiatry Hospital were initially informed about the treatment protocol and required to sign an informed consent form themselves or through their first-degree relatives. The patients were randomly assigned to either the intervention or control group by trained staff members who had no direct contact with the patients. In the intervention group, liothyronine (Sobhan drug co.) was administered at a dose of 0.5 micrograms per kilogram of the patient's weight for the first five days of the study, which was then increased to one microgram per kilogram. Drug administration began one day before the first ECT session and continued until one month after the last session. In the control group, a placebo produced by the same company was administered following the same protocol as the intervention group. Psychiatric and medical information, type of disorder, and demographic data were collected through structured clinical interviews.

Liothyronine appears to be a safe and effective alternative treatment for patients with mood and depression disorders when appropriate baseline and follow-up safety monitoring are implemented.[29]

Outcomes

The primary outcome measure was memory enhancement assessed using the Wechsler Memory Scale. Secondary outcomes included alterations in thyroid function measured through thyroid function blood tests.

ECT procedure

The ECT procedure was conducted three times a week using a current of 9/10 amperes, pulse duration of one millisecond, frequency ranging from 10 to 100 Hz, and bitemporal electrode placement in the bilateral method. The energy level started at 10 J in the first session and increased by 10 J in each subsequent session until reaching a maximum of 100 J. A seizure was induced in each session using Thiopental sodium at a dosage of 2-3 mg/kg for anesthesia induction. Patients continued their psychiatric medication as prescribed by their physician during the ECT sessions.

Memory assessment was conducted using the Wechsler Memory Test. A study by Orangi et al., reported the validity index of the Farsi version of this test to be between 0.28 and 0.98 for Wechsler memory subscales, consistent with Wechsler's reported validity index.[30] Due to limitations in patient resources and time constraints, only the subscales of visual memory, personal information, and associative learning were evaluated in this study.

Randomization

The patients were randomized into two groups using the permuted block randomization method. Randomization was performed by trained clinic staff using computer-generated random numbers to ensure blinding.

Sample size

A randomized clinical trial sample size calculation formula was used with a significance level (α) of 0.05, a power of 90% (β = 0.20), and a confidence interval of 95%. Based on similar studies, a minimum of 33 participants per group was calculated.

Statistical analysis

The Kolmogorov-Smirnov test was used to assess data distribution, while demographic differences between treatment groups were analyzed using independent-samples Chi-square tests. Repeated measures analysis was conducted with the Greenhouse-Geisser correction factor after verifying assumptions. The continuous variables were expressed as the mean±SD, and the categorical variables were presented as a percentage and frequency. All statistical analyses were performed with SPSS (version 16.0, SPSS Inc, Chicago, IL, USA). A "P-value" less than 0.05 was considered significant.

Ethical considerations

At the beginning of the questionnaire distribution session, the purpose of the study was explained to participants and they were assured about the anonymity and confidentiality of their responses. All participants gave their signed written informed consent letters. The study protocol was approved by the Ethics Committee of Kashan University of Medical Sciences "approval no. IR.KAUMS.REC.93183". All procedures performed in studies involving human participants were under the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. Clinical trial registration number; http://www.irct.ir: IRCT2015081823673N1

Results

Out of 100 screened patients with major depression and bipolar disorder, 66 patients were randomized into the intervention (n=33) or the placebo (n=33) groups. Figure 1 shows the CONSORT flow diagram detailing participant enrollment in the trial.

The descriptive characteristics of the participants are summarized in Table 1. There were no significant differences in basic characteristics among the subjects.

Prior to conducting the repeated measure analysis, the prerequisite assumptions were checked using Mauchly's and Box tests. The analysis of the current memory scale revealed a significant difference in mean scores across time intervals, F (2.18, 126.83) = 4.56, p=0.01. Additionally, there was a significant difference between the groups, F (2.18, 126.83) = 5.17, p<0.01, specifically observed before the final session time, where the intervention group had a lower score [Figure 2].

Subsequent analyses were performed on individual subscales of the WMS-R. The analysis of communicative learning indicated no significant effect of time, suggesting no notable difference between interval times or score trends. However, there was a significant difference between groups across interval times, F (1.67, 97.34) = 19.30, p<0.01. On the other hand, the analysis of communicative learning II demonstrated a significant effect of time, F (2.41, 142.64) = 4.18, p<0.01, indicating a significant difference between time intervals, particularly evident in the last measurement. Moreover, there was a significant difference between groups one month after measurement, F (2.41, 142.64) = 19.36, p<0.01 [Figures 3 and 4].

Regarding the visual memory I and II analysis, there were no significant differences across interval times for visual memory I, F (1.76, 102.05) = 0.41, p=0.63. However, a significant difference was observed for visual memory II, F (2.3, 133.56) = 4.42, p=0.01. In the between-group analysis of visual memory score I, a significant difference was noted between the intervention and placebo groups, with the intervention group showing a higher score, F (1.76, 102.05) = 17.14, p<0.01. This trend was consistent for visual memory II as well, with the intervention group scoring higher, F (2.3, 133.56) = 9.86, p<0.01 [Figures 5 and 6].

Discussion

This study highlights the specific role of liothyronine in treating ECT-induced amnesia by improving associative learning and visual memory in patients with mood disorders and bipolar disorder. The precise function of thyroid hormones in the adult brain remains unclear, but it is evident that impaired thyroid function can lead to cognitive decline, mood fluctuations, and psychiatric symptoms. Numerous studies have established a link

between cognition and thyroid health, showcasing reduced executive function efficiency, slower information processing, and learning difficulties.[31,32]

Despite the clinical benefits of ECT, some patients may be hesitant to initiate or continue treatment due to its well-documented cognitive side effects.[33] Liothyronine has been utilized to enhance ECT response rates, potentially reducing response time and cognitive complications when administered at the onset of an ECT regimen.[34] Previous studies have consistently supported these findings. For instance, Mousavi et al.'s study[18] assessing orientation, personal information, and mental control using the Wechsler memory test demonstrated that while ECT minimally impacted orientation, liothyronine administration post-ECT improved orientation without significant harm to other assessed subscales.

Table 1. Descriptive characteristics of participants[1]

Variables		Treatment arm N (%)	Control arm N (%)	P[2]
Age	18 to 39 years	19(57.5%)	16 (48.5%)	0.46
	40 to 45 years	14 (42.5%)	17 (51.5%)	
Gender	Female	18 (54.5%)	17 (51.5%)	0.80
	Male	15 (45.5%)	16 (48.5%)	
Education level	Primary school	4 (12.5%)	9 (27%)	0.26
	High school	21 (63.5%)	17 (51.5%)	
	Graduate/postgraduate	8 (24%)	7 (21.5%)	
Type of disorder	Major depression	13 (39.5%)	14 (42.5%)	0.80
	Bipolar disorder	20 (60.5%)	19 (57.5%)	

[1] Data are percentages. [2] Obtained from Pearson Chi-square test.

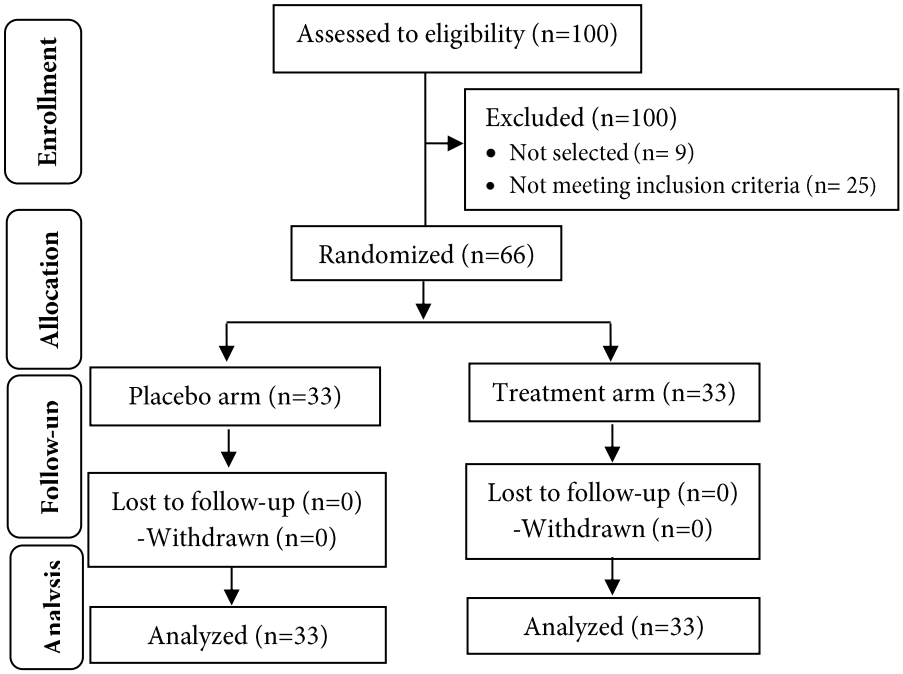

Figure 1. Summary of patient flow diagram

Figure 2. Within and between comparisons of current information scores across different time intervals.

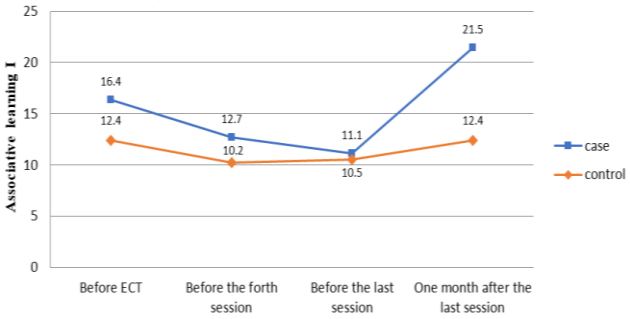

Figure 3. Within and between comparisons of associative learning I score across different time intervals.

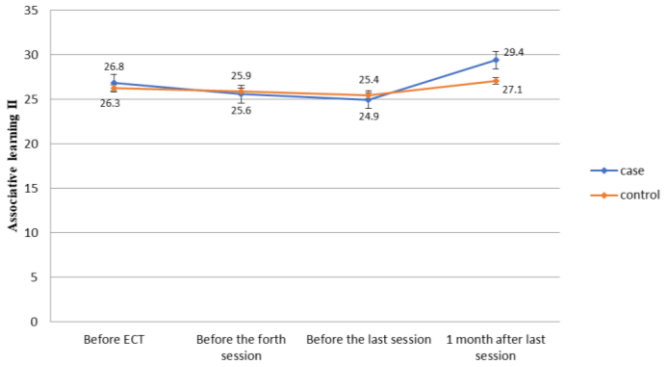

Figure 4. Within and between comparisons of associative learning II scores across different time intervals

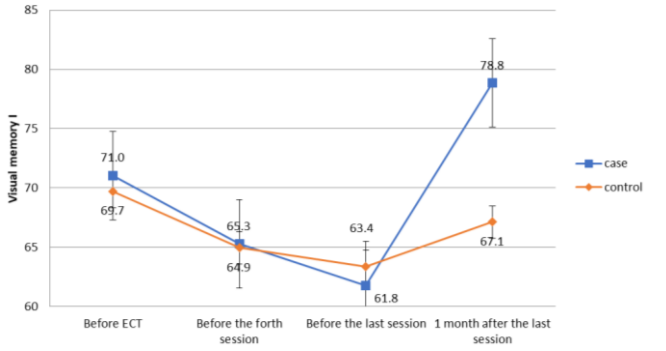

Figure 5. Within and between comparisons of visual memory I scores across different time intervals

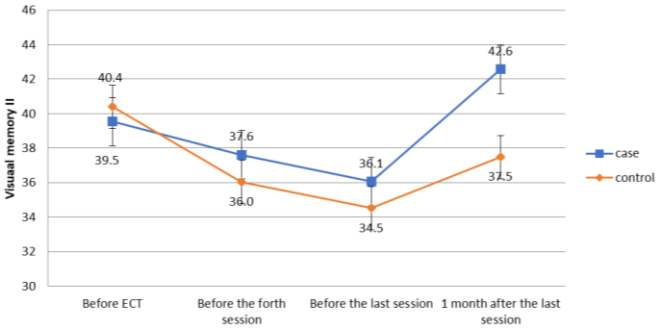

Figure 6. Within and between comparisons of visual memory II scores across different time intervals

Recent reports suggest that exogenous liothyronine may mitigate impaired peripheral T4 to T3 conversion caused by genetic variations, potentially expediting ECT response times.[18,35,36] Given the relative stability of this memory aspect compared to other cognitive functions, it appears that ECT's impact on personal information is limited, akin to its effects in dementia and delirium progression. Studies by Stern have shown memory improvements, particularly in remote memory and verbal learning, with liothyronine use.[35,37] Similarly, research by Mohagheghi indicated liothyronine's significant positive effects on verbal and visual memory, attention, concentration, and delayed recall.[27] Our study observed enhanced visual memory, aligning with Mohagheghi's findings. In another investigation involving patients with major depressive disorder, liothyronine not only improved depression symptoms but also enhanced cognition compared to the placebo group.[28] Conversely, Hamidi et al.'s study reported improved visual memory with liothyronine, possibly attributed to varying intervention strategies. Collectively, our study underscores liothyronine's beneficial role in mitigating ECT-induced amnesia, consistent with prior research on the subject.

There are various mechanisms suggesting how liothyronine exerts a positive effect. Firstly, it inhibits the anticonvulsive effects of TRH, lowering the convulsion threshold and subsequently reducing the amount of electrical stimulation received during ECT sessions. Secondly, it impacts the hypothalamus-pituitary-thyroid axis. Thirdly, it elevates serum levels of free thyroxin, decreasing ECT-induced amnesia. Lastly, it has a neuroprotective effect on memory and seizure-related neurons in the amygdala and hippocampus.[18,24]

While previous studies have demonstrated liothyronine's impact on ECT-induced amnesia, this study offers several advantages compared to previous studies. These include a larger sample size, closer patient monitoring during ECT, a one-month follow-up post-ECT, and evaluation of Wechsler memory test subscales not previously assessed.

Limitations of this study include not considering the number of ECT sessions as a factor affecting cognitive impairment, failure to measure thyroid hormone levels and changes as a variable, limited evaluation of Wechsler memory subscales due to patient non-cooperation, and continued use of prescribed medication out of ethical considerations and respect for the prescribing physician's opinion.

Conclusions

In conclusion, based on the results of this study, liothyronine shows promise in preventing ECT-induced amnesia and enhancing associative learning and visual memory in patients with mood disorders such as bipolar and depressive disorders who have undergone ECT. Further research on liothyronine is warranted for potential future applications.

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Competing interests

The authors declare that they have no competing interests.

Abbreviations

Electroconvulsive therapy: ECT;
Wechsler Memory Scale-Revised: WMS-R.

Authors' contributions

P.H, F.SGH, F.A, and A.GH contributed to the manuscript conception, design, statistical analysis, and drafting. P.H. and A.GH supervised the study. All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

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Role of the funding source

None.

Availability of data and materials

The data used in this study are available from the corresponding author on request.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. Institutional Review Board approval (code: IR.KAUMS.REC.93183) was obtained. The present study did not interfere with the process of diagnosis and treatment of patients and all participants signed an informed consent form. Clinical trial registration number; http://www.irct.ir: IRCT2015081823673N1

Consent for publication

By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

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