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Absence of cognitive impairment in patients undergoing ECT and concomitant treatment with lithium

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Dedicatória

À Doutora Luísa Maria C. T. Pinto Elyseu da Silva Violante gostaria de dedicar este trabalho que representa a conclusão de um princípio.
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Resumo

Objetivos: Várias guidelines preconizam que se evite terapêutica concomitante com lítio e electroconvulsivoterapia (ECT) uma vez que alguns estudos sugerem que o lítio tem um impacto cognitivo negativo pós-ECT e um risco acrescido de estados confusionais. No entanto, o lítio é um tratamento de eleição na perturbação bipolar e uma importante opção terapêutica no tratamento da depressão major resistente. Isto significa que comumente os doentes são aconselhados a suspender ou reduzir o lítio durante a realização de ECT, o que poderá acarretar com riscos acrescidos de recorrência do quadro psicopatológico. Assim, no presente estudo pretendemos avaliar o impacto cognitivo do lítio através do tempo de reorientação. Secundariamente, avaliámos o impacto do lítio na duração da convulsão motora e da convulsão segundo o eletroencefalograma (EEG).

Métodos: Este foi um estudo observacional prospetivo, tendo sido efetuada colheita de sangue antes de cada sessão para análise dos níveis séricos de lítio, hormonas tiroideias e ionograma. Os tempos decorridos desde a indução anestésica, à administração do estímulo elétrico e até ao momento de reorientação do doente foram registados em cada sessão, assim como a duração da convulsão motora e no EEG. Na análise estatística foi aplicado um modelo linear misto de modo a levar em conta a variabilidade dos dados no mesmo indivíduo e entre indivíduos e o ajustamento para potenciais confundidores.

Resultados: Dez participantes realizaram um total de 86 sessões (41% com localização unilateral direita e pulsos ultrabreves e 59% com localização bitemporal e pulsos breves). Nos doentes que realizaram ECT bilateral encontrou-se uma associação negativa entre o lítio e tempo de reorientação. Não se observou uma associação entre os níveis séricos de lítio e o tempo de reorientação nos indivíduos submetidos a ECT unilateral. Estes resultados foram observados mesmo após ajustamento para confundidores. Não se verificou uma influência significativa do lítio na duração da convulsão motora e no EEG.

Limitações: O estudo apresentou uma amostra reduzida, diminuindo o poder de teste nas comparações efetuadas. Não foi efetuada uma avaliação formal de estado confusional após as sessões. Os resultados obtidos não deverão ser extrapolados para níveis séricos de lítio >0.7 mmol/L.

Conclusão: Este estudo sugere que níveis séricos de lítio baixos a moderados (<0.7 mmol/L) não apresentam um impacto cognitivo relevante nos doentes submetidos a TEC unilateral (e pulsos ultrabreves) e poderão até apresentar um efeito protetor nos doentes que realizam TEC bilateral (e pulsos breves).

Palavras-chave

Lítio; Eletroconvulsivoterapia; Tempo de orientação; Disfunção cognitiva; Confusão.

Abstract

Objectives: Guidelines often warn against concomitant treatment with lithium and electroconvulsive therapy (ECT) as evidence suggests lithium has a negative cognitive impact in the recovery from ECT and a higher risk of delirium. However, lithium is considered to be a drug of choice when it comes to treat bipolar disease and resistant major depressive disorders. This means that patients are often required to stop taking their lithium medication before ECT, which poses relapse risks. In this study we examined the cognitive impact of serum lithium levels in patients undergoing ECT by measuring the reorientation time and also the effect of lithium in motor seizure duration and EEG seizure duration.

Methods: This study used an observational prospective approach. Blood samples were drawn before each ECT session to measure serum lithium levels, thyroid hormones and biochemical parameters. The time elapsed from the anesthetic induction to the electrical stimulus and then to the patients' reorientation was recorded in each session, as well as the motor seizure duration and EEG seizure duration. A statistical analysis using a linear mixed model was run in order to take into account both between and within individual variance while adjusting for confounding factors.

Results: Ten participants underwent a total of 86 sessions (41% right unilateral ultrabrief pulse, and 59% bilateral brief pulse). A negative interaction between serum lithium levels and reorientation time was found among patients doing bilateral brief pulse ECT. No association was observed in patients doing unilateral ultrabrief pulse ECT. These results were consistent when confounding factors were considered. No significant relationship was observed between lithium and both motor and EEG-assessed seizure duration.

Limitations: This study had a small sample size, which curtailed its comparative ability. No formal assessment of post-ECT confusional states was considered in this study. Conclusions from this study must not be assumed for serum lithium levels > 0.7 mmol/L.

Conclusion: This study suggests that low to moderate serum lithium levels (<0.7 mmol/L) are not associated with a significant cognitive impact in patients doing right unilateral ultrabrief pulse ECT, and may even show a protective effect in those undergoing bilateral brief pulse ECT. In addition, lithium didn't show any effect in seizure duration.

Keywords

Lithium; Electroconvulsive therapy; Orientation time; Cognitive dysfunction, Confusion.

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Acronym list

ACE	Angiotensin converting enzyme
BBB	Blood-brain barrier
BL	Bilateral
Cl-	Chlorine
CSF	Cerebrospinal fluid
CYP	Cytochrome P450
ECT	Electroconvulsive therapy
EEG	Electroencephalogram
GFR	Glomerular filtration rate
ICD-10	International classification of diseases, 10th revision
ICD-11	International classification of diseases, 11th revision
K+	Potassium
MMSE	Mini-mental status examination
Na+	Sodium
NSAID	Non-steroidal anti-inflammatory drug
RUL	Right unilateral
SD	Standard deviation
SE	Standard error
T3	Triiodothyronine
T4	Thyroxine
TSH	Thyroid stimulating hormone

1. Introduction

Electroconvulsive Therapy (ECT) is recommended for acute and maintenance treatment of mood and psychotic refractory disorders, as well as in acute emergent settings with evidence of a robust antisuicidal effect[1]. Its main adverse effect consists of cognitive impairment, such as acute transient disorientation, anterograde and retrograde amnesia[1]. As for lithium carbonate, it is the most widely studied mood stabilizer and a well-known first line acute and maintenance treatment for bipolar disorders[2] as well as an adjunctive pharmacological option for resistant depression[3]. It is also the mainstay of treatment for preventing relapse after an acute cycle of ECT. Its toxicity comprises a wide variety of symptoms, ranging from nausea and vomiting when mild, to coma, convulsions and collapse when severe[4]. Concomitant therapy with lithium and ECT is not infrequent: patients with unipolar depression or bipolar disorder medicated with lithium might be referred to ECT and, in patients for whom ECT was effective, lithium is strongly regarded as maintenance treatment option to prevent relapse after ECT[2].

The literature is vast respecting both lithium and ECT individually, but it's still lacking concerning their combined effects in terms of safety and risks regarding patients' neurocognitive function. Evidence in this matter consists mostly of case reports[5-16] as well as a few retrospective and naturalistic prospective studies. There is only one prospective controlled study regarding concomitant use of lithium and ECT[17]. Only recently a study has concluded that concomitant therapy is associated with a higher incidence of both acute delirium and transient cognitive impairment when compared to only ECT[18]. Due to the lack of consistency in the literature, both the Royal College of Psychiatrists[19] and the American Psychiatric Association's[20] guidelines advise for the withdrawal of lithium, or at least lowering its concentration to subtherapeutic levels, prior to starting ECT. Although some evidence is starting to emerge regarding the interaction between lithium and ECT, the path is still unclear as many times important confounders are not taken into account. We still lack certainty about which aspects influence post-ECT recovery, especially when the patient is also medicated with lithium carbonate. This leaves clinical practice with difficult decision-making situations. Should lithium be stopped at all before ECT (e.g. in a suicidal patient)? Should the dosage be reduced? If yes, how much? Reducing the dosage during the whole ECT cycle or just the day before each session? And when should it be started after an effective ECT cycle? A few sessions before ending the cycle or immediately after ECT (taking a few weeks until therapeutic level is achieved)? Finally, what about patients' ongoing maintenance ECT for years and benefiting also from lithium? Should lithium be permanently stopped? So, the recommendation to simply stop lithium seems detached from clinical practice and the need to deal with difficult-to-treat patients. The future of medicine and psychiatry is moving towards personalized care, which might mean, in the case of lithium and ECT, making fine decisions depending on clinical severity, previous lithium response, lithium and ECT effectiveness, side effects during each session, monitoring lithium levels, and also considering patient preferences.

This study aimed to assess the relationship between serum lithium levels and the reorientation time of patients under combination therapy while adjusting to potential confounders such as age, gender, type of ECT (unilateral or bilateral), anesthetic drug used, time interval between anesthetic induction and electrical discharge, charge, EEG seizure duration, motor seizure duration, titration session, TSH, T3, T4, sodium, potassium, and chlorine levels.

2. Methods

2.1 Setting and Subjects

The study took place at the ECT Unit of the Department of Psychiatry and Mental Health, Cova da Beira University Healthcare Center[a] (Covilhã, Portugal). ECT was offered both to inpatients and outpatients from the hospital's catchment area as well as from other hospitals not able to provide ECT.

All patients medicated with lithium therapy while undergoing ECT were recruited between May 2019 and January 2020 according to the study's selection criteria. These criteria were reviewed based on the patient's clinical records and charts. Selection criteria were: currently or about to enroll in ECT, age between 18 and 80 years, established ICD-10 or 11 diagnosis of major depressive disorder, bipolar disorder or other affective disorder, no use of NSAIDs, ACE inhibitors or calcium channel blockers within the last 48 hours, no excessive alcohol consumption nor recreational drug addiction, a mini-Mental Exam score of 22 or greater prior to ECT, absence of any sort of untreated thyroid or parathyroid dysfunction, uncontrolled hypertension, osteoporosis, previous diagnosis of diabetes insipidus, not undergoing treatment with CYP inducing (such as Carbamazepine or Rifampicin), or inhibiting drugs (such as Amiodarone, spironolactone, or ethinyl estradiol). Were excluded from the study patients who had a history of previously experiencing life threatening effects from either ECT or lithium carbonate intake (acute lithium toxicity, intracranial hypotension due to low cerebrospinal fluid (CSF) volume, or anesthesia-related adverse effects), renal impairment with GFR of ≤ 45 mL/min/1.73 m^2, and chronic users of NSAIDs, ACE inhibitors, or calcium channel blockers.

2.2 ECT procedure

At the ECT Unit where the study was performed, right unilateral electrode placement with ultrabrief pulses (RUL) was preferred except for severe cases, or when RUL was shown ineffective. In such severe cases (or RUL ECT ineffective) the patients underwent bilateral

[a] Translated from the its official name: Centro Hospitalar e Universitário da Cova da Beira

ECT with brief pulses (BL). Empirical titration was performed in the first session for all patients (except if very urgent ones) and charge was calculated at 6x seizure threshold for RUL ECT and 2.5x the seizure threshold for BL ECT. Both acute and maintenance ECT were offered. A MECTA spECTrum 5000Q device was used and patients were monitored with 2 channels EEG and 1 channel ECG. Thiopental was the anesthetic drug of choice although propofol had to be used instead in a few sessions due to a thiopental shortage. Succinylcholine and atropine were also administered in every session.

As part of routine care, extensive data was recorded in every ECT session. Of interest for the present study, a chronometer was started at anesthetic induction and time elapsed was recorded when the electrical stimulus was delivered, when the patient ventilated spontaneously and when the patient became reoriented. Full reorientation was referred as to obtaining the same score on the exact 5 questions as before the ECT session: name, age, present location, month, year. A nurse frequently asked the patient regarding these questions and when the pre and post-ECT scores were equal, the time elapsed since anesthesia would be recorded.

Adverse effects immediately after every ECT session were recorded and the patient was also asked before every ECT session regarding side effects between the last and present session, including cognitive impairment and confusion.

2.3 Study design

This was an observational prospective study assessing the correlation between serum lithium concentration and the time subjects would take to reorient themselves to person, time and space after the ECT procedure in a naturalistic approach. Secondarily, we also analyzed the correlation between both the motor and EEG seizure duration and the serum lithium levels in the same patients. Enrolled subjects would have blood samples drawn a few minutes before entering the ECT room where the procedure would take place.

2.4 Ethical considerations and statement of interest

Due to its naturalistic observational design no changes of any sort were made in the patients' treatment solely for the purpose of this study. Written informed consent regarding the study's design, details and how their data, clinical notes and charts would be handled was obtained from each patient. The study protocol has been reviewed and approved by the review board of the ethics committee of Cova da Beira University Healthcare Center.

This study required no funding of any kind and its authors declare no conflict of interest nor affiliations with involvement in any organization or entity with financial or non-financial interest in either the subject matter or materials of this study.

2.5 Variables

Biochemical, ECT-related, and sociodemographic variables such as age and gender were collected. Serum lithium, thyroid stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), sodium (Na+), potassium (K+), and chlorine (Cl-) levels were assessed via laboratorial analysis. Reorientation time was used as a surrogate marker for assessing the relationship between combined therapy with lithium plus ECT and the patients' post-ictal cognitive impairment, as evidence suggests longer reorientation times to be associated with greater retrograde amnesia[(21)]. Time elapsed between anesthesia and the stimulus, motor seizure time, and EEG seizure time were measured using a digital stopwatch, as well as reorientation time. Gender, age, anesthetic drugs, ECT modality, titration sessions, and delivered stimulus charge were assessed directly from the subjects' clinical files.

2.6 Statistical analysis

Statistical analysis was performed with SPSS version 25 (IBM). The effect of serum lithium on reorientation time was analyzed using Linear Mixed Effects Models with level 1 accounting for the ECT session and level 2 for the patients. Both the intercept and the slope were included as random effects in the model. A bivariate analysis was first run in order to assess the variables' behavior in terms of slope and intercept for each patient before fitting a multilevel model. A step-up approach was used in the multilevel analysis for finding the best fitting model.

3. Results

There was a total of 10 patients from the Cova da Beira Central University Hospital enrolled in the study which corresponded to a total of 114 ECT sessions. Twenty four of these entries were excluded due to incomplete data. Four of the remaining 90 reported a reorientation time >1 hour (3600 seconds) and were considered outliers, ending up being excluded, as in those specific cases patients actually fell asleep during the recovery. This rendered a total of 86 valid ECT sessions. Table 1 describes the sample's demographic features and the number of ECT sessions each patient went through. Table 2 represents the sample's distribution according to the selected clinical characteristics of the study. These results refer to patients whose serum lithium levels were mostly within 0.1 and 0.7 mmol/L (92%). Only 3 were first (titration) sessions.

Table 1- Age, sex and number of sessions, by patient

Patient #	Age	Gender	Number of sessions (%)
1	50	F	10 (11.6)
2	60	F	8 (9.3)
3	60	F	9 (10.5)
4	64	F	10 (11.6)
5	59	F	7 (8.1)
6	65	F	26 (30.2)
7	68	F	9 (10.5)
8	38	F	2 (2.3)
9	55	M	4 (4.7)
10	42	F	1 (1.2)
Total			86 (100)

Table 2 - Distribution of the sample's characteristics

Parameter		Number of session (%)		
Electrode placement modality	Unilateral	35 (41)		
	Bilateral	51 (59)		
Anesthetic drug used	Thiopental	77 (89)		
	Propofol	9 (11)		
Titration session	No	83 (96)		
	Yes	3 (4)		
	Mean	SD	Minimum	Maximum
Age (in years)	56	10	38	68
Delivered charge (in mC)	316	190	19	704
EEG seizure time (in seconds)	29	12	0	65
Motor seizure time (in seconds)	18	9	0	50
Serum lithium levels (in mmol/L)	0.40	0.20	0.06	1.23
Time between anesthetic induction and stimulus (in seconds)	194	25	131	308
Time between the stimulus and patient's reorientation (in seconds)	1714	701	614	3523
Serum TSH levels (in uUI/mL)	3.1	2.5	0.9	21.6
Serum T3 levels (in pg/mL)	2.6	0.6	1.4	3.9
Serum T4 levels (in ng/dL)	0.9	0.2	0.7	1.5
Serum Na+ levels (in mmol/L)	140	4	112	148
Serum K+ levels (in mmol/L)	4.4	0.3	3.5	5.2
Serum Cl- levels (in mmol/L)	103	4	82	110

In a bivariate analysis serum lithium levels did not show an association with time to reorientation. Delivered charge showed a significant positive correlation with reorientation time (B= 1.2; p= 0.015). Regarding the type of anesthetic use, thiopental was associated with a significantly higher time to reorientation (B=598; p=0.007). No other variables showed significant associations with time to reorientation (table 3).

Table 3 - Bivariate analysis of the impact of ECT and patient factors on reorientation, motor seizure and EEG seizure times using an individual linear mixed model for each variable

	Reorientation time			**Motor seizure time**			**EEG seizure time**		
	Estimate	S.E.	p-value	Estimate	S.E.	p-value	Estimate	S.E.	p value
ECT session factors									
Lithium	-226	372	p>0.05	-3.9	4	p>0.05	-5.1	7.2	p>0.05
ECT charge	**1.2**	**0.5**	**0.015**	-0.0002	0.009	p>0.05	0.006	0.015	p>0.05
RUL	-811	123	p>0.05	-1.2	3	p>0.05	0.9	5	p>0.05
BL*	-	-	-	-	-	-	-	-	-
Thiopental	**598**	**220**	**0.007**	3	2.6	p>0.05	-4	4	p>0.05
Propofol*	-	-	-	-	-	-	-	-	-
Titration	123	311	p>0.05	0.7	4	p>0.05	-4	8	p>0.05
TSH	68	70	p>0.05	-0.9	0.9	p>0.05	0.1	1.5	p>0.05
T3	50	177	p>0.05	5.2	1.2	p>0.05	4.6	2.7	p>0.05
T4	-436	471	p>0.05	18	4	0.1	12	111	p>0.05
Na	21	16	p>0.05	0.1	0.3	p>0.05	0.2	0.4	p>0.05
K	15	222	p>0.05	-2	3	p>0.05	2.5	4	p>0.05
Cl	-11	18	p>0.05	0.2	0.3	p>0.05	0.3	0.4	p>0.05
Patient factors									
Age	17	16	p>0.05	-0.1	0.2	p>0.05	-0.4	0.4	p>0.05
Female	-357	321	p>0.05	-10	4	p>0.05	-1.4	6	p>0.05
Male*	-	-	-	-	-	-	-	-	-

*reference category

Subsequently, a multivariate linear mixed model was performed with time to reorientation as the outcome. A baseline model was obtained showing a calculated variance partition coefficient of 0.33, which means that patient individual differences accounted for about 33% of the variation in reorientation time. Patients were introduced as a random effect and several ECT session level variables were introduced as fixed effects using a step-up approach. The best fitting model is represented in Table 4.

Table 4 - Impact of serum lithium levels and other variables on reorientation time

	Reorientation time		
Parameter	Estimate	SE	p-value
Serum lithium levels	-1078	448	0.018
RUL	-814	157	<0.001
BL (reference)	-	-	-
Thiopental	698	188	<0.001
Propofol (reference)	-	-	-
Lithium*RUL interaction	1447	576	0.014

*reference;
Excluded variables: Age, gender, ECT charge, time elapsed between the anesthesia and the stimulus, titration session, TSH, T3, T4, sodium levels, potassium levels, and chlorine levels; Results shown according to the best fitting model obtained from a step-up approach using a multilevel analysis (Likelihood ratio chi-square = 29.8; df = 8; p<0.001).

We observed that lithium presented a significant negative relationship with the patients' reorientation time only when its interaction with the ECT placement modality was considered in the model. The interaction between lithium and the ECT modality was found to play a significant role and to better examine this relation figures 1 and 2 are presented, showing for RUL ECT no clear tendency regarding the effect of lithium levels on reorientation but, in contrast, for BL ECT a consistent decrease in reorientation time as lithium levels increased. For each 0.1 mmol/L of serum lithium increase, patients on BL ECT took on average 145 seconds (2'25'') less to recover. Figure 2 illustrates the representative model of the above mentioned.

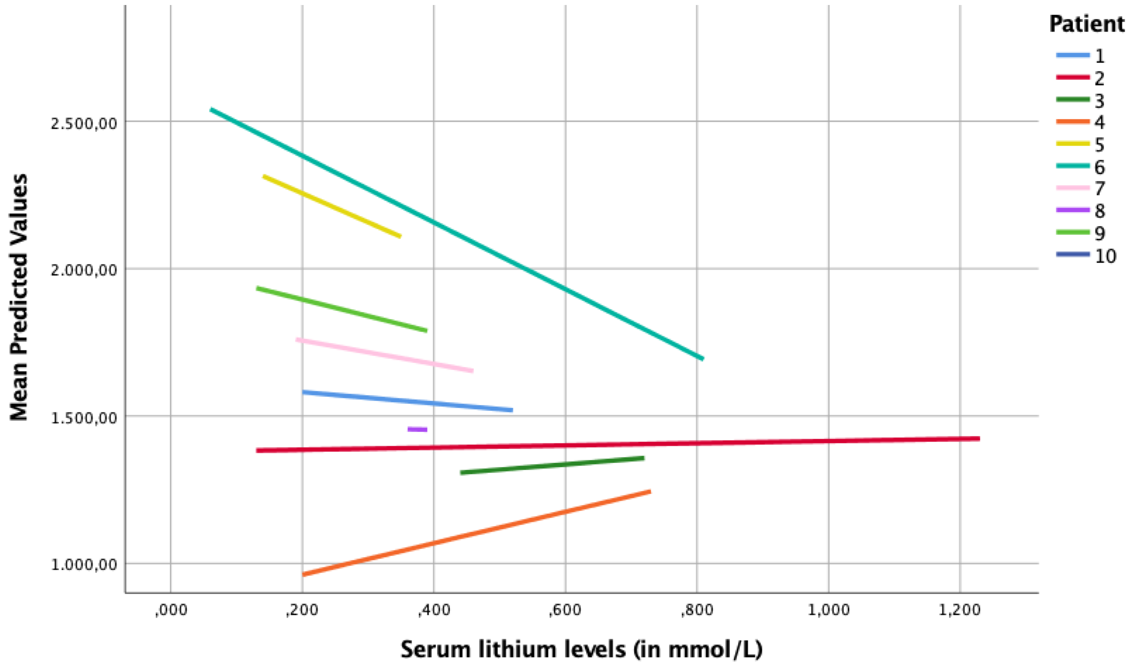

Figure 1 - Correlation of serum lithium and reorientation time for each patient

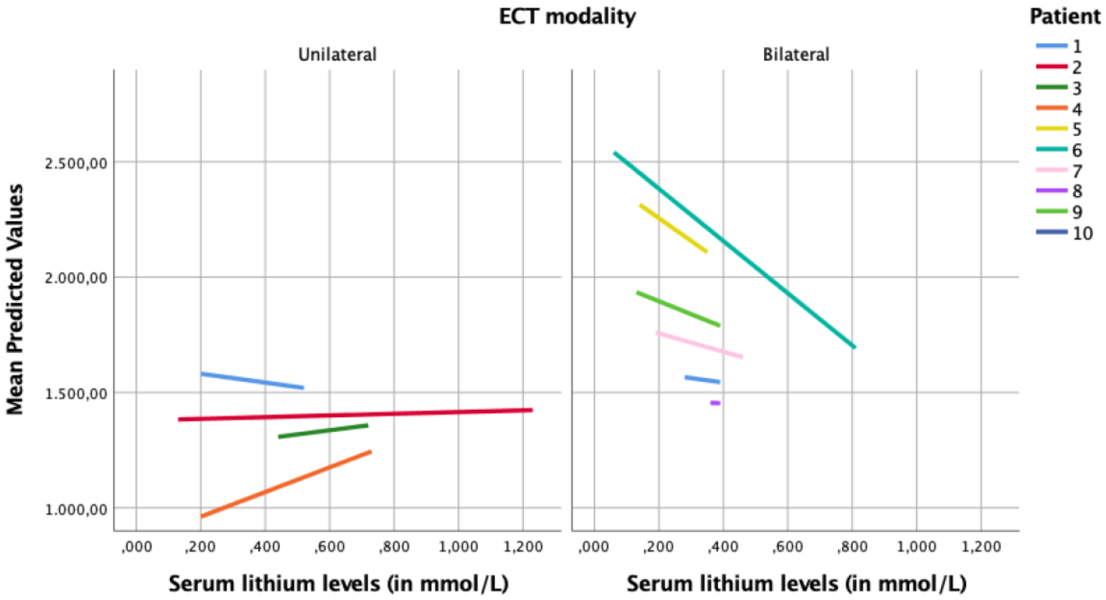

Figure 2 - Correlation of serum lithium and reorientation time for each patient, split by ECT modality

It was also found that patients submitted to RUL ECT took approximately 814 seconds (13'34'') less to reorientation than patients under BL ECT.

Regarding the anesthetic drug used, thiopental resulted in a recovery time of about 698 seconds (11'38'') longer when compared to propofol.

No significant model was obtained regarding motor seizure time and EEG seizure time.

Of note, no post-ictal acute confusional state or clinically evident level of cognitive impairment was reported after any of the presented ECT sessions, either by hospital personnel, the patient or caregivers.

4. Discussion

The most striking finding of this study was to observe a negative correlation between serum lithium levels and the patients' reorientation time, which only presented as statistically significant when considering an interaction with the ECT modality. By assessing the serum lithium levels of patients undergoing BL ECT (and 1.0 ms brief pulses), we noticed that those with higher levels actually recovered faster from the procedure than those with lower levels. For those under RUL ECT (and 0.3 ms ultrabrief pulses) we found no influence of lithium in reorientation time. This relationship may be better perceived by analyzing the slopes of different patients when split by ECT type (figure 2). This observation completely contradicted our expectations and is the first study to ever report such results. Previous authors have suggested either a positive correlation or no correlation at all[7, 17, 18, 22], but there are no mentions whatsoever about a negative relationship between these two variables, although no literature addressed specifically the interaction between lithium and the ECT modality.

Despite the lack of research studies mentioning this, there are some case reports that comment on the occurrence of adverse effects even in patients with subtherapeutic lithium levels[11, 15, 16, 23], and El-Mallakh has also expressed some theoretical concerns in his review regarding the fact that ECT may enhance central manifestations of lithium toxicity with therapeutic or even subtherapeutic levels, pointing out ECT as a plausible early trigger of lithium toxicity[24]. In terms of physiology, a transient blood-brain barrier (BBB) breach caused by an intra-ictal hypertensive surge has been held responsible for the causative mechanism of some cognitive side effects such as amnesia due to the dispersion of circulating substances in the blood to the cerebral spinal fluid, though it is still unknown what substances are mostly implicated[25]. Normal diffusion of lithium into the brain occurs mainly based on the serum levels and also the length of exposure to the drug. In addition, lithium levels in the CSF are usually lower than in serum, with brain to serum ratios as low as 0.5 mmol/L[26, 27], although significant variation seems to occur along the 24-hour day cycle[27], with lower ratios in the morning. Finally, ECT-induced increase in blood-brain barrier permeability may allow serum lithium to diffuse in larger amounts to the CSF, leading to the usual neurotoxic manifestations seen with higher serum lithium levels. However, this remains speculative and a study using animal models has not been able to demonstrate a statistically significant elevation of CSF lithium levels following ECT[11].

A key remark of the present study is its sample's serum lithium levels, which were mostly within a low range, between 0.1 and 0.7 mmol/L, seemingly reflecting psychiatrists' concerns with lithium plus ECT related side effects but at the same maintaining patients on lithium therapy. The recommended therapeutic dosage of lithium for acute treatment aims at reaching serum levels between 0.8 and 1.2 mmol/L[2], although for depression lower levels might be indicated, or in maintenance therapy, where 0.4 to 1 mmol/L has been advocated to be sufficient, with a benign side effect profile[2, 28]. So, in spite of the fact that most of our subjects had lithium levels in the low range, the first hypothesis we could think of for possibly justifying such an observation would be of lithium not presenting a genuine linear relationship with the recovery time but actually a curved one. In fact, there is emerging evidence suggesting that lithium may even pose as a neuroprotective and neurotrophic drug in patients with bipolar disease, although not for every subtype of the disease[29]. This protective effect might not be exclusive for mood disorders, but having a more generalized effect, as lithium has also been studied for its potential in Alzheimer's disease[30]. This would determine that low lithium levels could actually be a protective factor against cognitive post-ECT cognitive impairment, and thus a negative correlation would be found until a certain threshold would be reached and patients would start exhibiting longer reorientation times as they would have higher lithium levels. However, this is purely speculative and would require further investigation under a different study design.

The study also found that bilateral electrode placement was associated on average with a longer reorientation time. Patients on bilateral brief ECT took about 13 minutes and 34 seconds longer than those on right unilateral ultrabrief ECT to reorient themselves. This observation is consistent with the literature[31], as bilateral electrode placement has been associated with a higher proportion of adverse effects[1, 22], even though it has been associated with better clinical outcomes in patients with depression[1].

Regarding the anesthetic drug used to induce sleep during the ECT procedure, thiopental was significantly associated with a longer recovery time, when compared to propofol, of about 11 minutes and 38 seconds. This observation is also very much consistent with the existing literature[32, 33], and no significant interaction between serum lithium levels and the anesthetic drug was found.

In terms of age and gender, there was no clear relationship between subjects' reorientation time, although evidence tells it otherwise. A study of Patel and associates has described a 12 times higher susceptibility for individuals above 60 years old to become acutely delirious and 6-fold higher odds of developing some sort of mild cognitive impairment following combined therapy of lithium and ECT when compared to those without lithium[18], although dosages and serum levels were not reported. It has also been described that people of geriatric age have a higher prevalence of post-ECT cognitive impairment[1] and that those who are older than 50 years old may have incremental risk of presenting signs of lithium toxicity[4].

Regarding EEG-assessed and motor seizure times, evidence points out that subjects taking lithium may be more prone to prolonged seizures, especially EEG-assessed when compared to observed motor seizures[17, 34]. However, we did not find any significant relation between either observed motor or EEG-assessed seizure duration with the subjects' serum lithium levels. EEG measuring is an operator dependent task which is determined on the basis of the clinician's experience interpreting EEGs, and may leave this variable somewhat prompt to operator bias.

Also, no thyroid parameter or electrolytic ion was found to have a significant impact in the patients' reorientation time, though there has been some evidence suggesting that the use of T3 in patients recovering from ECT may in fact improve their cognitive impairment, disregarding of their previous thyroid function. Interestingly enough, positive findings have shown that T3 may be used to improve the cognitive function of patients taking lithium, which has led some authors to propose the use of adjunctive treatment with thyroid hormones in order to minimize the negative cognitive effects of lithium and ECT[35].

The main shortcomings of this study were related to its structural design as it was subject to the many weaknesses inherent to naturalistic studies. Also, the absence of a control group, the small sample size, overrepresentation of females, were all limitations that might have influenced our results. Also, it is important to mention that this study used the patients' reorientation time as a surrogate marker for the relationship between combined therapy and cognition. No formal assessment of delirium after ECT was considered for the purpose of this study. This means that, since most of the literature, except for one study[18], addresses the above-mentioned clinical manifestations as their main outcome variables, our observations may not reflect the exact same clinical outcomes as most studies. However, reorientation time seems to be a good predictor of medium and long term cognitive function after ECT[21] and might even be a more relevant marker than a transient side effect such as post-ictal confusional states.

While this study adds a new perspective for interpreting the combination of ECT with lithium it has also disclosed some of the uncertainty inherent to the field. It remains to be seen if these observations can be replicated in other studies and further research is still needed regarding different lithium levels under ECT with both unipolar and bipolar electrode placement (and different pulse durations) in order to bridge this chasm of the true impact lithium has in patients under ECT. As evidence is still scant we suggest that one should exercise caution whenever combining both therapies. However it should be borne in mind that concomitant ECT and lithium might not necessarily need to be contraindicated and such recommendations may actually present more harm than benefit in some patients. It might be plausible to consider maintaining lithium in some patients despite concomitant ECT, especially if bilateral (brief pulses) ECT. What needs to be crucial is exercising a precise and tailor-made treatment for each patient, as lithium has a low therapeutic margin, meaning that in low to moderate dosages it has a therapeutic, and possibly even neuroprotective, but at slightly higher levels it becomes neurotoxic. Monitoring lithium levels along the ECT cycle should be a fundamental step, with target levels in the lower therapeutic bound (0.4-0.7 mmol/L), meaning that even during transient ECT induced BBB increase in permeability, there would be enough room before neurotoxic levels are reached.

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6. Annex

6.1 Ethical committee's approval

Centro Hospitalar Cova da Beira,EPE

IMPRESSO

Parecer da Comissão de Ética para a Saúde

Código: CHCB.IMP.COMET.01 | *Edição:* 5 | *Revisão:* 0

Parecer nº: 19/2019	**Data:** 2019-04-24
Assunto: Estudo nº 12/2019 - "Avaliação do Impacto Cognitivo do Lítio em Doentes Submetidos a Terapia Electroconvulsiva"	

Membros da CES do CHCB:

Prof. Doutor Manuel Passos Morgado (Presidente, Farmacêutico)

Dra. Ana Paula Torgal Carreira (Vice-Presidente, Assistente Social)

Dr. Luís Manuel Ribeiro (Médico)

Enf. Maria Gabriela Ramalhinho (Enfermeira)

Dra. Maria Teresa Bordalo Santos (Psicóloga)

Dr. Luís Manuel Carreira Fiadeiro (Jurista)

Dr. António Luciano Costa (Teólogo)

Ex.mo Senhor Investigador
Ricardo Miguel Martins Ascenção

A Comissão de Ética para a Saúde do Centro Hospitalar Universitário Cova da Beira, em reunião realizada em 2019.04.24 deliberou emitir parecer relativamente à realização do Estudo nº 12/2019 - "Avaliação do Impacto Cognitivo do Lítio em Doentes Submetidos a Terapia Electroconvulsiva".

Membros da CES do CHUCB presentes:

Prof. Doutor Manuel Passos Morgado
Dra. Ana Paula Torgal Carreira
Enf. Maria Gabriela Ramalhinho
Dra. Maria Teresa Bordalo Santos

Parecer:

Apreciado o projeto e os esclarecimentos adicionais remetidos, foi decidido por unanimidade dos votantes emitir parecer favorável à realização do estudo proposto.

Este parecer não dispensa a necessária autorização por parte do Ex.mo Conselho de Administração do CHUCB quanto à concretização do estudo, nem eventuais requisitos ou procedimentos por parte do Responsável pelo Acesso à Informação (RAI) ou do Encarregado de Proteção de Dados (EPD) desta instituição, no âmbito do cumprimento do previsto no Regulamento Geral sobre a Proteção de Dados (RGPD) e/ou noutra legislação aplicável quanto a acesso, tratamento e proteção de dados.

O Presidente da CES do CHUCB

(Prof. Doutor Manuel Passos Morgado)

Página: 1 de 1

6.2 Hospital's research and development office's approval

REPÚBLICA PORTUGUESA
SAÚDE

SNS SERVIÇO NACIONAL DE SAÚDE

Centro Hospitalar Cova da Beira, EPE

23 MAIO 2019

Assunto:Projecto de Investigação n.º 12/2019-"Avaliação do Impacto Cognitivo do Lítio Submetidos a	
Para:Exmo. Sr. Presidente do Conselho de Administração	Nº: 39/2019
De:Gabinete de Investigação e Inovação	Data:23-05-2019

Em relação ao assunto em epígrafe, junto envio o pedido de Ricardo Miguel Martins Ascenção, aluno do curso de Mestrado Integrado em Medicina da Faculdade de Ciências da Saúde da Universidade da Beira Interior, para a realização de um estudo subordinado ao tema "Avaliação do Impacto Cognitivo do Lítio Submetidos a Terapia Electroconvulsiva", a realizar no Departamento de Psiquiatria e Saúde Mental deste Centro Hospitalar.

Envio ainda o parecer nº 19/2019, emitido pela Comissão de Ética para a Saúde do Centro Hospitalar Universitário Cova da Beira.

Informo que se encontram reunidos todos os requisitos necessários de acordo com o Regulamento e Procedimentos do Centro de Investigação Clínica.

Com os melhores cumprimentos,

A Coordenadora do Gabinete de Investigação e Inovação,

(Dr.ª Rosa Saraiva)

RS/MA

Centro Hospitalar Cova da Beira
Presente em reunião de C.A.
Em 23 MAIO 2019
Despacho De acordo