Impact of the anesthetic-to-electric stimulus time interval in patients undergoing electroconvulsive therapy

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Dedicatória

À mente… Ao deslumbrante universo que a dimensão humana não compreende completamente…

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A todo o ser humano especial que guardo em proximidade...

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Preface

"If you can't explain it simply,

You don't understand it well enough."

Albert Einstein

Resumo

Introdução: Os fármacos utilizados na anestesia em eletroconvulsivoterapia (ECT) possuem efeito anticonvulsivo que pode reduzir a qualidade e a duração da convulsão. O intervalo de tempo entre a indução anestésica e o estímulo elétrico tem sido investigado, recentemente, devido à possível influência sobre o tratamento, uma vez que determina indiretamente a concentração cerebral de anestésico no momento da estimulação elétrica. Neste estudo, avaliou-se o impacto do intervalo decorrido entre a indução anestésica e o estímulo elétrico sobre os parâmetros no eletroencefalograma (EEG) e a duração motora das convulsões, em pacientes submetidos a eletroconvulsivoterapia.

Métodos: Este é um estudo observacional retrospetivo, em que os indicadores de qualidade da convulsão no EEG (duração, estereotipia, regularidade, supressão pós-ictal e qualidade global) e a duração de convulsão motora observável foram previamente registados e, posteriormente, avaliados por um psiquiatra. A análise estatística foi realizada com Modelos Lineares de Efeitos Mistos, avaliando a relação do intervalo de tempo anestésico-a-estímulo elétrico com variáveis de resultado, ajustada para potenciais fatores confundidores.

Resultados: Incluíram-se 42 pacientes e um total de 490 sessões de eletroconvulsivoterapia. Mostrou-se um impacto positivo de um maior intervalo de tempo anestésico-a-estímulo elétrico em todos os parâmetros do EEG (melhor estereotipia, regularidade, supressão pós-ictal e qualidade global da convulsão) e na duração de convulsão motora.

Limitações: Além dos possíveis vieses de dados e de operador pela natureza retrospetiva do estudo, não foram controladas variáveis como o efeito da ventilação nem das medicações habituais dos doentes.

Conclusão: Demonstrou-se que um maior intervalo de tempo entre a indução anestésica e o estímulo elétrico tem um impacto positivo na qualidade da ECT. Desta forma, propõe-se a definição e difusão de um procedimento personalizado de determinação dos intervalos de tempo entre indução anestésica e o relaxante muscular ou o estímulo elétrico para cada doente.

Palavras-chave

Terapia electroconvulsiva; indução anestésica; estímulo elétrico; qualidade da convulsão; reorientação

Abstract

Introduction: Drugs used for anesthesia in electroconvulsive therapy (ECT) have anticonvulsant properties that can affect seizure quality and duration. The anesthetic-to-electric stimulus time interval has been recently researched due its possible influence on treatment efficacy since it indirectly determines the brain concentration of anesthetic at the time of electric stimulation. In this study, we assessed the impact of the anesthetic-to-electric stimulus (ATES) time interval on EEG parameters and motor seizure duration, in patients undergoing ECT.

Methods: This is an observational retrospective study, in which seizure quality parameters on EEG (duration, stereotypy, regularity, postictal suppression, and global quality) and seizure motor duration were previously recorded and then analyzed by a psychiatrist. Statistical analysis was performed with Linear Mixed Effects Models to assess the relationship between anesthetic-to-electric stimulus time interval on outcome variables, adjusting for potential confounding factors.

Results: Forty-two patients and 490 ECT sessions were included in this study. A positive impact of a longer anesthetic-to-electric stimulus time interval was found in all EEG parameters (increased stereotypy, regularity, postictal suppression, and global seizure quality) and in motor seizure duration.

Limitations: Besides possible data and operator bias inherent to the retrospective design, variables such as pretreatment ventilation and the effects of patient medication were not controlled.

Conclusion: We demonstrated that longer anesthetic-to-electric stimulus time interval had a positive impact on ECT quality. Therefore, we defend a personalized procedure for determination of time intervals between anesthetic induction and muscle relaxant or electric stimulus for each patient.

Keywords

Electroconvulsive therapy; anesthetic induction; electric stimulus; seizure quality; reorientation

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Acronym List

ATES	Anesthetic-to-electric stimulus
BT	Bitemporal
DSM-5	Diagnostic and statistical manual of mental disorders, 5th edition
ECG	Electrocardiogram
ECT	Electroconvulsive therapy
EEG	Electroencephalogram
Est	Estimate
RUL	Right unilateral
SE	Standard error
SPSS	Statistical Package for the Social Sciences

1. Introduction

Electroconvulsive therapy (ECT), which consists of administering electric stimulation to induce a seizure under anesthesia, is a medical procedure for the treatment of severe psychiatric disorders (1–13). It is considered lifesaving for patients in need of urgent therapy (3,12) (like those with feeding refusal, catatonic features and high risk of suicide) or presenting refractory conditions (1,7,9,10,13–16). Nonetheless being used for a long time, the exact therapeutic mechanism is not completely understood (3,11,13), only known to involve multifactorial changes in cerebral blood flow, neuron signal transduction and regional metabolism (7).

Despite decades of progress, ECT remains under social (or medical) stigma (7,13) and is less prescribed than it should (10,17). Nowadays, it can significantly improve the health-related quality of life in patients of both sexes and at all ages (5).

Loss of autobiographical memory and short-term impairment in new learning, also known as retrograde and anterograde amnesia, were the most relevant adverse effects related with ECT (1,8,10,11,18). Acute confusion and postictal disorientation are common immediately after the session (10) and could exist a correlation between time to orientation post-treatment and loss of autobiographical memory at 2 months after the course of ECT (8).

Based on their negative pretreatment expectations, some patients attribute preexisting subjective memory impairment to ECT (19). Although, when assessed before and after the session, subjective memory improved more often than worsened (19).

The effectiveness of ECT correlates with great seizure quality, defined by a higher peak slow wave amplitude, increased slow-wave regularity, intense seizure activity and an abrupt seizure suppression (14,20). These can be influenced by factors like the anesthetic drugs and pretreatment ventilation. Seizure quality also seems to decrease throughout the treatment course itself, due to a rise in seizure threshold (4,15,21).

An ideal induction anesthetic should have short half-life, rapid action, minor hemodynamic changes and no interference with seizure threshold or duration (2,6,11,22). Almost all anesthetics used in ECT have anticonvulsant properties (1,4,14,15,22,23) that can affect seizure spreading in the brain tissue (20,23). Advantages like rapid recovery, short-duration confusion, and low incidence of adverse reactions (like hypertension or tachycardia) make propofol and thiopental extensively used in this context (1,23).

Propofol contributes to rapid onset and recovery with less hemodynamic change, although simultaneously increases seizure threshold and reduces seizure duration (2,6,11).

Thiopental, a barbiturate drug, has superiority over propofol in respect to lesser anticonvulsant effect, longer seizure duration (2,14,23) and possibly lesser cognitive impact (6), although it may cause nausea and arrhythmias like sinus bradycardia or premature ventricular beats (6).

Ventilation with 100% oxygen before anesthetic induction until recovery of spontaneous breathing is a standard recommendation, given the almost 200% increase of oxygen consumption during seizure (22). However, pretreatment hyperventilation is also used to induce hypocapnia, which could have a seizure facilitating effect (17).

The time interval between anesthetic induction and electric stimulation will determine anesthetic's concentration in the brain at the time of the stimulus (15,17,20,21). If this concentration is high, anticonvulsant effects may reduce the capacity to induce seizure. Following the bolus, anesthetic levels peak in the plasma, rapidly penetrate the blood-brain barrier (21), and sedate in 15 to 40 seconds (24,25). Recent data suggests that a longer time lapse until electric stimulation could improve seizures (14,15,17,20,21). Therefore, taking ATES time interval into account could avoid unnecessary increase of electric charges (17) or switch of ECT modalities as well as their higher side-effect risks (21). However, if ATES time interval is too long, the risk of patient awareness and inadequate muscle relaxation increases as well (15,17). Given the simplicity of this measure, some studies claimed its clinical monitorization and individual interpretation (14,15,20,21).

Our preliminary hypothesis is that a longer ATES time interval leads to better outcomes, superior seizure length and better seizure quality, and it may also affect the time needed for reorientation after the ECT session. This study aims to determine the influence of ATES time interval on seizure quality, seizure duration and patient reorientation time-length, adjusted for potential confounders, such as age, sex, anesthetics, stimulus charge, electrode placement and pulse width.

2. Material and Methods

2.1 Study design

This is an observational retrospective study using data from all ECT sessions performed between August 2018 and December 2020 at two different ECT units in Portugal.

2.2 Population

We included data from patients older than 18 years and a suitable diagnosis for treatment with acute or maintenance ECT (Major Depressive Disorder with or without psychotic features, Bipolar disorder, Obsessive-Compulsive disorder, Schizophrenia and other, according to DSM-5 classification).

We excluded cases in which anesthetics other than thiopental or propofol were used. Titration sessions were also excluded, as the parameters are considerably different than subsequent sessions.

2.3 ECT and anesthetic procedures

Before the first ECT session, patient medication is reviewed and stopped as much as possible. Only antidepressant medication and benzodiazepines are sometimes maintained in a minimal acceptable dose. Other anticonvulsant medications are completely stopped.

Following practice guidelines (1), patients begin with empirical seizure threshold estimation in the first session (titration). Optimal charge following treatment is calculated as six-fold for RUL modality and 2.5-fold for BT modality. This charge is subsequently adjusted according to psychopathological improvement and EEG trace parameters. Modality choice and pulse duration is made favoring brief pulse (0.5 ms and 1.0 ms) and BT placement for efficacy and ultra-brief pulse and RUL placement for side effects prevention. By default, RUL and ultra-brief pulses were preferred. The course of ECT treatment was considered complete based on clinical judgement and clinical results.

Anesthesia with thiopental (3-5mg/kg) or propofol (1-2mg/kg) is, optionally, preceded by atropine, to prevent post-ECT bradyarrhythmia, and followed by muscle relaxation with succinylcholine (0.5mg/kg). Pretreatment oxygenation and hyperventilation are performed, mostly the first option. Electric stimulus was administered using a MECTA spectrum 5000Q device with three control channels: 2 for EEG and 1 for ECG.

Time lapse between anesthetic bolus administration and electric stimulus delivery, as well as stimulus-to-spontaneous breathing time lapse and stimulus-to-reorientation time lapse are recorded with a stopwatch. Recovery of awareness is monitored in the observation room by the nurse. Reorientation is considered as the ability of the patient to correctly answer to protocol questions after procedure – name, age, month, year, and location.

We collected data comprising thiopental, propofol and succinylcholine's doses (mg); stimulus charge (mC); electrode placement (RUL or BT); pulse width (0.3, 0.5 or 1.0 ms); ATES time interval (min); stimulus-to-spontaneous breathing time interval (min); stimulus-to-reorientation time interval (min); and motor seizure duration (sec).

2.4 EEG procedure and analysis

After alcohol cleansing, electrodes are placed on frontal and mastoid regions bilaterally and monitoring starts. ECG and EEG traces are automatically registered by the MECTA EMR© software.

A psychiatrist experienced in ECT blindly assessed the EEG and classified the parameters according to a scale previously used in other studies (14,15,20). The indices considered were stereotypy (0-3), regularity (0-6), postictal suppression (0-3), global seizure quality (1-5), seizure duration on EEG trace (sec) and observable motor seizure duration (sec).

2.6 Statistical analysis

Statistical analysis was performed using SPSS version 26 (IBM). ATES and stimulus-to-reorientation time intervals were converted in seconds for the analysis.

First, a logarithm base 10 transformation of the data was performed to get a normal distribution and deem the data suitable for analysis. Separate mixed models were run for the seven dependent variables to estimate the independent variable behavior both as a random or fixed factor. The ATES time interval was introduced in the model as a random factor for all the further analysis. Subject was included as a random effect for each dependent variable and each one of the covariates.

The influence of ATES time interval on EEG stereotypy, postictal suppression, trace regularity, global seizure quality, motor and EEG duration, and reorientation time was analyzed with Linear Mixed Effects Models controlling for factors that could potentially affect seizure expression: age (years), sex (female=0), anesthetic (thiopentone/propofol mg), pulse width (ms), charge (mC), and electrode placement (RUL=1/BT=2).

Statistical tests were two-tailed, and significance was set at $p<0.05$.

2.7 Ethical considerations

This study was reviewed and approved by the Local Ethics Committee of both study sites. Patients signed an informed consent form before the procedures. The need for a new consent form for this anonymized retrospective study was dismissed.

3. Results

A total of 545 ECT sessions from 43 patients were initially retrieved. Forty-six titration sessions were excluded and nine sessions with no seizure occurrence were rejected, rendering 490 ECT sessions for thorough analysis.

Demographic, clinical and ECT session variables are described in Table 1. As depicted, patients were mostly female (79%) and with an average 58 years of age. Major depressive disorder was the most frequent diagnosis, with nonpsychotic features in 55% and with psychotic features in 24%. Thiopental was the most used anesthetic (92% of sessions) and RUL ultra-brief pulses were the most used ECT technique (66% of sessions). Motor seizure mean duration was 22 seconds and EEG seizure mean duration was 35 seconds. ATES time interval was on average 3 minutes and 20 seconds; time to spontaneous breathing was 2 minutes and 28 seconds; and time to reorientation was approximately 25 minutes.

Table 2 presents a bivariate statistical analysis, with one-by-one comparison between the main predictor (ATES time interval)/confounders and the dependent variables. A significant association between ATES time interval and all outcomes, such as EEG parameters (duration, stereotypy, regularity, postictal suppression, and global quality), motor seizure duration and time to reorientation was observed.

Table 1 - Sample's characteristics

Patient variables (n=42)	
Age (years), *mean (SD)*	58 (12)
Sex, *n (%)*	
Female	33 (79)
Male	9 (21)
Diagnosis, *n (%)*	
Major depressive disorder	23 (55)
Major depressive disorder psychotic	10 (24)
Bipolar disorder	4 (10)
Obsessive compulsive disorder	2 (5)
Schizophrenia	1 (2)
Other	2 (5)

Table 1 - Sample's characteristics (continuation)

ECT session variables (n=490)	
Anesthetic dose (mg), *n (%)*	
Thiopental	453 (92)
Propofol	37 (8)
Delivered charge (mC), *mean (SD)*	213 (135)
Pulse width (msec), *n (%)*	
0.3ms	323 (66)
0.5ms	16 (3)
1.0ms	151 (31)
Type of treatment, *n (%)*	
Acute	442 (90)
Maintenance	48 (10)
Electrode placement, *n (%)*	
RUL	324 (66)
BT	166 (34)
Anesthetic-to-electric stimulus time interval (sec), *mean (SD)*	202 (66)
Electric stimulus – Spontaneous Breathing (sec), *mean (SD)*	148 (74)
Electric stimulus – Reorientation (sec), *mean (SD)*	1514 (898)
Motor seizure duration (sec), *mean (SD)*	22 (11)
EEG seizure duration (sec), *mean (SD)*	35 (16)
Stereotypy (0-3), *mean (SD)*	2.0 (0.9)
Regularity (0-6), *mean (SD)*	4.4 (1.3)
Postictal suppression (0-3), *mean (SD)*	2.0 (0.8)
Global seizure quality (1-5), *mean (SD)*	3.4 (1.2)

Using a linear mixed-effects approach, the best fitting model was performed for each dependent variable (Table 3). As shown, even after adjustment for potential confounders (age, sex, anesthetic drug, total electric charge, pulse width and electrode placement), ATES time interval had a positive impact on all the outcome variables: a longer ATES time interval related to higher stereotypy, stronger postictal suppression, enhanced regularity as well as improvement in global seizure quality. It was also associated with longer EEG trace seizure duration, motor seizure duration and time to reorientation.

Table 2 - Bivariate analysis between the dependent variables, covariates, and the independent variable (ATES time interval)

	Stereotypy			Regularity			Postictal suppression			Global quality		
	Est	SE	p	Est	SE	p	Est	SE	p	Est	SE	p
Patient factors												
Age	-0.016	0.009	0.080	-0.016	0.010	p>0.05	**-0.021**	**0.008**	**0.010**	-0.019	0.011	0.090
Sex[1]	0.099	0.271	p>0.05	-0.178	0.354	p>0.05	-0.242	0.236	p>0.05	-0.338	0.326	p>0.05
ECT session factors												
Anesthetic[2]	0.165	0.217	p>0.05	**-0.472**	**0.221**	**0.033**	**0.330**	**0.141**	**0.019**	0.098	0.203	p>0.05
Pulse	-0.200	0.262	p>0.05	-0.380	0.271	p>0.05	-0.211	0.166	p>0.05	-0.302	0.248	p>0.05
Charge	-0.001	0.001	p>0.05	-0.000	0.001	p>0.05	-0.108	0.225	p>0.05	-0.001	0.001	p>0.05
Electrode placement[3]	0.135	0.176	p>0.05	**0.411**	**0.178**	**0.021**	0.197	0.110	0.074	-0.292	0.163	0.074
ATES time interval[4]	**0.033**	**0.011**	**0.003**	**0.069**	**0.021**	**0.001**	**0.030**	**0.010**	**0.001**	**0.058**	**0.017**	**0.001**

Note. [1] Reference value: Female = 0; [2] Reference value: Propofol = 0; [3] Reference value: Unilateral = 0; [4] seconds. * Logarithm base 10 transformation. For each dependent variable, an individual linear mixed model was used.

Table 2 - Bivariate analysis between the dependent variables, covariates, and the independent variable (ATES time interval) (continuation)

	Motor seizure			EEG seizure			Reorientation		
	Est	SE	p	Est	SE	p	Est	SE	p
Patient factors									
Age	-0.004	0.002	p>0.05	-0.003	0.003	p>0.05	0.003	0.002	p>0.05
Sex[1]	-0.008	0.065	p>0.05	0.017	0.085	p>0.05	**0.106**	**0.051**	**0.047**
ECT session factors									
Anesthetic[2]	-0.036	0.033	p>0.05	0.046	0.032	p>0.05	**-0.167**	**0.030**	**0.000**
Pulse	-0.020	0.042	p>0.05	-0.044	0.042	p>0.05	**0.260**	**0.027**	**0.000**
Charge	**-0.000**	**0.052**	**0.002**	**-0.000**	**0.091**	**0.022**	0.002	0.236	p>0.05
Electrode placement[3]	-0.022	0.027	p>0.05	-0.051	0.027	0.059	**-0.086**	**0.025**	**0.001**
ATES time interval[4]	**0.002**	**0.001**	**0.000**	**0.023**	**0.006**	**0.000**	**0.851**	**0.005**	**0.000**

Note. [1] Reference value: Female = 0; [2] Reference value: Propofol = 0; [3] Reference value: Unilateral = 0; [4] seconds. * Logarithm base 10 transformation. For each dependent variable, an individual linear mixed model was used.

Table 3 - Impact of the ATES time interval on seizure parameters and reorientation - Linear Mixed Effects Models

	Stereotypy			Regularity			Postictal suppression			Global quality		
Covariate	Est	SE	p	Est	SE	p	Est	SE	p	Est	SE	p
ATES time interval[4]	**0.055**	**0.017**	**0.002**	**0.075**	**0.023**	**0.001**	**0.020**	**0.008**	**0.009**	**0.055**	**0.017**	**0.009**
Age	**-0.019**	**0.010**	**0.049**	-0.015	0.013	p>0.05	-0.016	0.008	0.051	-0.018	0.011	p>0.05
Sex[1]	0.157	0.258	p>0.05	-0.170	0.359	p>0.05	-0.254	0.214	p>0.05	0.031	0.311	p>0.05
Anesthetic[2]	0.142	0.215	p>0.05	**0.483**	**0.215**	**0.025**	0.260	0.216	p>0.05	0.111	0.199	p>0.05
Pulse	0.484	0.799	p>0.05	1.026	0.596	0.086	0.601	0.495	p>0.05	0.684	0.549	p>0.05
Charge	-0.000	0.001	p>0.05	0.000	0.001	p>0.05	-0.001	0.001	p>0.05	-0.000	0.001	p>0.05
Electrode placement[3]	0.441	0.542	p>0.05	**1.103**	**0.390**	**0.005**	0.512	0.326	p>0.05	**0.721**	**0.359**	**0.045**

Note. [1] Reference value: Female = 0; [2] Reference value: Propofol = 0; [3] Reference value: Unilateral = 0; [4] seconds. * Logarithm base 10 transformation. Best fitting linear mixed model analyzing the impact of ATES time interval on outcomes, adjusted for potential confounding variables.

Table 3 - Impact of the ATES time interval on seizure parameters and reorientation - Linear Mixed Effects Models (continuation)

	Motor seizure			EEG seizure			Reorientation		
Covariate	Est	SE	p	Est	SE	p	Est	SE	p
ATES time interval[4]	**0.002**	**0.001**	**0.001**	**0.005**	**0.001**	**0.000**	**0.725**	**0.162**	**0.000**
Age	-0.003	0.002	p>0.05	-0.002	0.003	p>0.05	-0.001	0.001	p>0.05
Sex[1]	0.011	0.060	p>0.05	0.065	0.083	p>0.05	**-0.313**	**0.036**	**0.000**
Anesthetic[2]	-0.035	0.032	p>0.05	0.453	0.031	p>0.05	-0.004	0.004	p>0.05
Pulse	0.093	0.090	p>0.05	0.155	0.089	0.081	-0.013	0.011	p>0.05
Charge	**-0.000**	**0.000**	**0.002**	-0.000	0.000	0.057	0.014	0.027	p>0.05
Electrode placement[3]	0.040	0.058	p>0.05	0.126	0.057	0.027	-0.004	0.007	p>0.05

Note. [1] Reference value: Female = 0; [2] Reference value: Propofol = 0; [3] Reference value: Unilateral = 0; [4] seconds. * Logarithm base 10 transformation. Best fitting linear mixed model analyzing the impact of ATES time interval on outcomes, adjusted for potential confounding variables.

4. Discussion

As hypothesized, we found that a longer ATES time interval has a significant impact on seizure quality. All EEG parameters and motor seizure duration improved with longer intervals between anesthetic induction and electric stimulus, both in bivariate analysis and multivariate linear mixed models controlling for several potential confounders. This shows a highly consistent association of ATES time interval with seizure quantitative and qualitative parameters, pointing to a probable causal effect. Additionally, we verified that with longer ATES time interval, time to reorientation also increased.

Thus, the administration of electric stimulus when the anesthetic brain concentration is higher might produce seizures with inferior quality than if it is administered after peak levels have passed (20,21). As reorientation time is related with seizure duration, and longer ATES time interval with an increase in seizure duration, this might explain the observed increase in that time.

Despite ECT's long history and large body of research, the discussion on the importance of ATES time interval is recent. This time interval only been actively studied in latest years, with findings that it has a significant impact in several seizure parameters (14,15,17,21). Gálvez et al. (2016) found that longer ATES time interval lead to higher scores in amplitude, regularity, stereotypy and postictal suppression as well as longer seizure duration (20). Also, Taylor et al. (2019), in a study with thiopentone, found a significant impact of ATES time interval on ictal EEG quality indices with longer intervals resulting in increased amplitude, enhanced postictal suppression and superior general seizure quality (14), without a significant influence in regularity, seizure duration or orientation scores after ECT (14). More recently, in 2020, a study described higher amplitude, postictal suppression, regularity, general seizure quality and seizure duration associated with longer ATES time interval (15).

Nonetheless, despite quite homogenous results across previous studies and our study with data from almost 500 ECT sessions, to our knowledge, there are no guidelines addressing the importance and use of the ATES time interval.

Regularity, postictal suppression and stereotypy are features of the EEG that might be used to assess how the seizure initiates, spreads into the brain and finishes (20). In the literature, more intense seizure activity and more abrupt postictal suppression are indicators of better efficacy outcomes (9), namely greater antidepressant response (20).

Also, there is an important relationship between the maintenance of symptomatic improvement and seizure quality (16). The American Psychiatric Association stated the absence of postictal suppression or a low EEG seizure amplitude can be an evidence for the need to increase stimulus dosage to reach adequate responses to ECT (9,26).

ECT seizure duration, either motor or on EEG trace, can be a moderate predictor of the treatment success (2,11,22,23), and consequently a good marker to assess. While some studies indicate that seizures less than 15 seconds may not be clinically effective (7), others affirm there is no set time related to effectiveness (9).

A study assessing the time to reorientation as a predictor of short-term treatment outcome found that patients with longer times to reorientation met the remission criteria after fewer treatments (26). Otherwise, a prolonged reorientation time has been reported as a predictor of subsequent retrograde amnesia (14,27,28). Martin et al. (2015) demonstrate that reorientation time during ECT course was the strongest predictor of retrograde autobiographical memory changes at post ECT (1,18).

As secondary findings we found seizure quality was also influenced by age, sex, anesthetic, charge, and electrode placement. However, we should, again, point to the fact that the ATES time interval showed, apparently, a much more consistent impact on seizure parameters than other well-established factors (age, charge, pulse width and electrode placement).

Certain disagreement exists about what is the most appropriate anesthetic to be used in ECT, and few literatures focus on these drugs pharmacokinetics despite its possible influence. It is referred that the effects of thiopental and propofol on seizure threshold and duration seem to be dose-dependent (4,29), with propofol having stronger anticonvulsant properties than thiopental (14,20). In several studies, thiopental was associated with longer seizure duration (2,23) and propofol associated with shorter times to reorientation (18,23). ECT units included in this study use thiopental as the standard anesthetic, with propofol being used only as an alternative in a period of thiopental shortage. Due to significant differences in brain kinetics among anesthetic used in ECT, the best predicted ATES time interval will also be different.

Our results are in line with the recommendation given by Gálvez et al. (2016) that to reduce the anticonvulsant anesthetics effects on seizure expression, the ATES time interval should be extended to as long as possible (20,22), avoiding deep anesthesia during ECT treatments, but simultaneously pondering the risks of awareness

(12,14,17,20) and postictal agitation (29). A recent study set a ATES time interval of 2 minutes and 30 seconds and obtained good results, without excessive need of second anesthetic administration (15).

In the present study, thiopental was the most frequently anesthetic used. This anesthetic is a highly lipophilic molecule and easily crosses the blood-brain barrier (24). According to studies in animals, following intravenous administration, this drug reaches its peak brain concentration in about 1 minute (24). The rate of penetration into the brain is limited only by the rate of cerebral blood flow with concentrations slightly lower than in plasma (24). In distribution phase, it equilibrates rapidly in highly perfused organs like the central nervous system and, subsequently, between these organs and adipose tissue (24). It is thought that recovery from clinical anesthesia is due mainly to redistribution of the drug than its metabolism (30). Thus, we can infer that if electric stimulus is administered following the peak time and some time after the start of distribution phase, less anticonvulsant effect is expected, and better seizure parameters can be seen.

Actual guidelines recommend decisions regarding dosing adjustment during ECT to be based mostly on serial monitoring of seizure duration and quality in the EEG, highlighting the importance of optimizing all factors with possible influence in seizure parameters (15). As mentioned above, although not part of current best practice recommendations, ATES time interval should be included as an essential variable to consider. The best interval might not be the same for every individual as factors such as age, weight, sex and others are known to interfere with the pharmacokinetics of anesthetic and, consequently, seizure parameters.

Taken together, our results show the importance of implementing a rigorous timetable protocol for each patient to maximize seizure quality (14,15,17,20), improve ECT efficacy, increase treatment predictability, avoid inefficient ECT treatment sessions and prevent adverse effects of random ATES time intervals. Recent findings even suggest that genetic variation might modulate interindividual variation of the ECT response (13), so taking all the individual factors in consideration will certainly lead to better outcomes.

Although monitoring the ATES time interval is easy to implement, setting that time might not be so easy in practice. If one is to adopt a fixed ATES time interval, this must imply that muscle relaxation is complete and the patient ready for stimulus delivery, which might not happen due to unexpected factors, leading to the necessity of anticipating or delaying stimulus delivery. An option would be to set a fixed time interval between anesthetic induction and muscle relaxant administration, which most probably remains unchanged across sessions. This is the current strategy used in one of the ECT units included in this study. A hybrid alternative may also be possible: if seizure quality and duration in the preceding session were good enough, we would follow the set time between anesthetic and muscle relaxant and, if possible, deliver the electric stimulus at the same exact time as previously.

Setting the time between anesthetic induction and muscle relaxant administration or electric stimulus delivery, as referred above, can have a major relevance on the predictability of seizure parameters. Once achieved, a timing that led to good or optimal seizure duration and quality, should be set for that patient during the whole ECT cycle, until degradation of seizure quality or unwanted changes occur, such as awareness. Thus, using a fixed time interval simultaneously flexible according to the patient´s needs, may be an important and feasible procedure to implement in the near future.

We can point out a few strengths of our study. First, a large dataset was used, including all sessions performed during a specific time interval. Second, two different ECT units were included, with significant differences, such as personnel, hospital type, context and geographical area. Additionally, statistical analysis was remarkably homogeneous using bivariate analysis and after controlling for confounders using linear mixed methods modelling.

Limitations include its retrospective design, with possible data retrieval. Patients regular medications were maintained during ECT, however anticonvulsants were stopped and benzodiazepines were reduced in patients having higher dosages, as detailed in the Methods section. Although the possible effect of the drug interactions on seizure generation and parameters cannot be overlooked (1,16,31), there is no formal indication to suppress regular medication given the relatively rare interaction of the ECT with commonly prescribed psychotropic drugs (31). Moreover, the titration session might compensate for this effect if medication is kept stable along the treatment course (32). Pretreatment ventilation parameters was not collected. Studies suggest longer hyperventilation can enhance seizure production, increase neuromuscular excitability (1), improve seizure duration, reduce charge and decrease time to reorientation (15,17,21,22), possibly due to the lower levels of carbon dioxide (which has anticonvulsant properties) achieved at the time of stimulus administration (14). Nonetheless, no significant effects on ictal seizure quality were found (15). Also, hyperventilation use is controversial as it produces change in cerebral blood flow (33). Ictal amplitude and time to slow wave onset, previously reported in literature, was not assessed as seizure quality indicators in our study (14–17).

5. Conclusion

ATES time interval had a consistent and remarkable impact on seizure quality and duration. As these are related to clinical outcomes, our study demonstrates the importance of standardizing and lengthening the time interval between anesthetic induction and electric stimulus (or muscle relaxant) during the ECT procedure. Controlling for longer ATES time intervals could allow more effective and predictable ECT sessions.

Determining the best ATES time interval and strategies for implementation in clinical practice could be next steps to explore in future studies.

6. References

1. Weiss A, Hussain S, Ng B, Sarma S, Tiller J, Waite S, et al. Royal Australian and New Zealand College of Psychiatrists professional practice guidelines for the administration of electroconvulsive therapy. Aust N Z J Psychiatry. 2019;53(7):609–23.

2. Jarineshin H, Kashani S, Fekrat F, Vatankhah M, Golmirzaei J, Alimolaee E, et al. Seizure Duration and Hemodynamic State During Electroconvulsive Therapy: Sodium Thiopental Versus Propofol. Glob J Health Sci. 2015;8(2):126–31.

3. Delamarre L, Galvao F, Gohier B, Poulet E, Brunelin J. How Much Do Benzodiazepines Matter for Electroconvulsive Therapy in Patients with Major Depression? J ECT. 2019;35(3):184–8.

4. Gálvez V, Hadzi-Pavlovic D, Smith D, Loo CK. Predictors of seizure threshold in right Unilateral Ultrabrief electroconvulsive therapy: Role of concomitant medications and anaesthesia used. Brain Stimul. 2015;8(3):486–92.

5. Güney P, Ekman CJ, Hammar Å, Heintz E, Landén M, Lundberg J, et al. Electroconvulsive therapy in depression: Improvement in quality of life depending on age and sex. J ECT. 2020;36(4):242–6.

6. Canbek O, Ipekcioglu D, Menges OO, Atagun MI, Karamustafalioglu N, Cetinkaya OZ, et al. Comparison of propofol, etomidate, and thiopental in anesthesia for electroconvulsive therapy: A randomized, double-blind clinical trial. J ECT. 2015;31(2):91–7.

7. Salik I; Marwaha R. Electroconvulsive Therapy [Internet]. 2020 [updated 2020 Nov 29; cited 2021 Jan 27]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538266/

8. Porter RJ, Baune BT, Morris G, Hamilton A, Bassett D, Boyce P, et al. Cognitive side-effects of electroconvulsive therapy: what are they, how to monitor them and what to tell patients. BJPsych Open. 2020;6(3):1–7.

9. Francis-Taylor R, Ophel G, Martin D, Loo C. The ictal EEG in ECT: A systematic review of the relationships between ictal features, ECT technique, seizure

threshold and outcomes. Brain Stimul. 2020;13(6):1644–54.

10. Kellner CH, Obbels J, Sienaert P. When to consider electroconvulsive therapy (ECT). Acta Psychiatr Scand. 2020;141(4):304–15.

11. Stripp TK, Jorgensen MB, Olsen NV. Anaesthesia for electroconvulsive therapy - New tricks for old drugs: A systematic review. Acta Neuropsychiatr. 2018;30(2):61–9.

12. Jorgensen A, Christensen SJ, Jensen AEK, Olsen N V., Jorgensen MB. The influence of the anesthesia-to-stimulation time interval on seizure quality parameters in electroconvulsive therapy. J Affect Disord. 2018;231(December 2017):41–3.

13. Pinna M, Manchia M, Oppo R, Scano F, Pillai G, Loche AP, et al. Clinical and biological predictors of response to electroconvulsive therapy (ECT): a review. Neurosci Lett. 2018;669:32–42.

14. Taylor R, Hadzi-Pavlovic D, Nikolin S, Bull M, Wark H, Leyden J, et al. The anaesthetic-ECT time interval with thiopentone—Impact on seizure quality. J Affect Disord. 2019;252(December 2018):135–40.

15. Taylor R, Wark H, Leyden J, Simpson B, McGoldrick J, Hadzi-Pavlovic D, et al. Effects of the Anaesthetic-ECT time interval and ventilation rate on seizure quality in electroconvulsive therapy: A prospective randomised trial. Brain Stimul. 2020;13(2):450–6.

16. Minelli A, Abate M, Zampieri E, Gainelli G, Trabucchi L, Segala M, et al. Seizure adequacy markers and the prediction of electroconvulsive therapy response. J ECT. 2016;32(2):88–92.

17. Kadiyala PK, Kadiyala LD. ECT: A new look at an old friend. Curr Opin Anaesthesiol. 2018;31(4):453–8.

18. Martin DM, Gálvez V, Loo CK. Predicting retrograde autobiographical memory changes following electroconvulsive therapy: Relationships between individual, treatment, and early clinical factors. Int J Neuropsychopharmacol. 2015;18(12):1–8.

19. Sigström R, Nordenskjöld A, Juréus A, Clements C, Joas E, Pålsson E, et al.

Long-term subjective memory after electroconvulsive therapy. BJPsych Open. 2020;6(2):1–7.

20. Gálvez V, Hadzi-Pavlovic D, Wark H, Harper S, Leyden J, Loo CK. The Anaesthetic-ECT Time Interval in Electroconvulsive Therapy Practice - Is It Time to Time? Brain Stimul. 2016;9(1):72–7.

21. Gálvez V, Loo CK. Clinical applicability of monitoring the time interval between anesthesia and electroconvulsive therapy. J ECT. 2017;33(1):4–6.

22. Kadiyala PK, Kadiyala LD. Anaesthesia for electroconvulsive therapy: An overview with an update on its role in potentiating electroconvulsive therapy. Vol. 61, Indian Journal of Anaesthesia. Indian Society of Anaesthetists; 2017. p. 373–80.

23. Nuzzi M, Delmonte D, Barbini B, Pasin L, Sottocorna O, Casiraghi GM, et al. Thiopental is better than Propofol for electroconvulsive therapy. Acta Biomed. 2017;88(4):450–6.

24. National Center for Biotechnology Information. PubChem Compound Summary for CID 3000715, Thiopental [Internet]. 2004 [cited 2021 Apr 11]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Thiopental.

25. National Center for Biotechnology Information. PubChem Compound Summary for CID 4943, Propofol [Internet]. 2016 [cited 2021 Apr 10]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Propofol.

26. Magne Bjølseth T, Engedal K, Šaltyte Benth J, Bergsholm P, Strømnes Dybedal G, Lødøen Gaarden T, et al. Speed of recovery from disorientation may predict the treatment outcome of electroconvulsive therapy (ECT) in elderly patients with major depression. J Affect Disord. 2016;190:178–86.

27. Kolshus E, Jelovac A, McLoughlin DM. Bitemporal v. high-dose right unilateral electroconvulsive therapy for depression: A systematic review and meta-analysis of randomized controlled trials. Psychol Med. 2017;47(3):518–30.

28. Martin D, Katalinic N, Hadzi-Pavlovic D, Ingram A, Ingram N, Simpson B, et al. Cognitive effects of brief and ultrabrief pulse bitemporal electroconvulsive therapy: A randomised controlled proof-of-concept trial. Psychol Med.

2020;50(7):1121–8.

29. Kronsell A, Nordenskjöld A, Bell M, Amin R, Mittendorfer-Rutz E, Tiger M. The effect of anaesthetic dose on response and remission in electroconvulsive therapy for major depressive disorder: nationwide register-based cohort study. BJPsych Open. 2021;7(2):1–6.

30. Brandon RA, Baggot JD. The pharmacokinetics of thiopentone. J Vet Pharmacol Ther. 1981;4(2):79–85.

31. Anderson IM. Interactions between ECT and Prescribed Medication. In: Ferrier IN, Waite J, editors. The ECT Handbook. 4th ed. Cambridge: Cambridge University Press; 2019. p. 218–33.

32. Janjua AU, Dhingra AL, Greenberg R, McDonald WM. The Efficacy and Safety of Concomitant Psychotropic Medication and Electroconvulsive Therapy (ECT). CNS Drugs. 2020;34(5):509–20.

33. Gómez-Arnau J, de Arriba-Arnau A, Correas-Lauffer J, Urretavizcaya M. Hyperventilation and electroconvulsive therapy: A literature review. Gen Hosp Psychiatry. 2018;50(September 2017):54–62.

7. Appendix

7.1 Ethical committee's approval

IMPRESSO

Centro Hospitalar Cova da Beira,EPE

Parecer da Comissão de Ética para a Saúde

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

Parecer nº: 45/2020	**Data:** 2020.07.28
Assunto: Estudo nº 46/2020 - "Impact of the anesthetic-to-electric stimulus time interval in patients undergoing electroconvulsive therapy"	

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)

Exma. Senhora Investigadora
Raquel Oliveira Inácio

A Comissão de Ética do Centro Hospitalar Universitário Cova da Beira, em reunião realizada em 2020.07.28 deliberou emitir parecer relativamente à realização do Estudo nº 46/2020 - "Impact of the anesthetic-to-electric stimulus time interval in patients undergoing electroconvulsive therapy"

Membros da CE do CHUCB presentes:

Prof. Doutor Manuel Passos Morgado
Dra. Ana Paula Torgal Carreira
Dra. Maria Teresa Bordalo Santos
Dr. Luís Manuel Ribeiro
Dr. Luís Manuel Carreira Fiadeiro

Parecer:

Apreciado o projeto do estudo, foi decidido por unanimidade dos votantes emitir parecer favorável à sua realização, com a seguinte observação: "o parecer emitido pela Comissão de Ética do CHUCB apenas é aplicável a sua realização nesta instituição, devendo nas outras instituições ser solicitado à Comissão de Ética respetiva".

Este parecer não dispensa 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 previsto no Regulamento Geral sobre a Proteção de Dados (RGPD) ou noutra legislação aplicável quanto a acesso, tratamento e proteção de dados.

A realização do estudo carece da necessária autorização por parte do Exmo. Conselho de Administração do CHUCB e no seu decurso pode ser sujeito a auditorias.

O Presidente da CE do CHUCB

(Prof. Doutor Manuel Passos Morgado)

Página: 1 de 1

7.2 Hospital administration's approval

Boa tarde,

Concordo com a realização do estudo e sugiro a inclusão clara do Hospital de Neurociências do TSHCVC nos trabalhos publicados, tese, posters, comunicações orais e artigos (assim como plano de tese); e que os mesmos sejam disponibilizados à instituição,

Ao dispor,

Melhores Cumprimentos | Best Regards

José Vila Nova

CMO
Vice Presidente do Conselho de Administração

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