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## **Delaying initiation of electroconvulsive treatment after administration of the anaesthetic agent and muscle relaxant reduces the necessity of re-stimulation**

**Running title:** Timing of ECT after thiopental and succinylcholine administration

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## Abstract

### Objectives

To investigate the effect of delaying initiation of electroconvulsive therapy (ECT) after administration of anaesthetic agent and muscle relaxant.

### Methods

A retrospective cohort study utilizing a case-based analysis comparing number of re-stimulations, length of seizures, number of ECTs per series and stimulation dosage before and after introducing a new treatment regimen. In 2013, ECT was initiated approximately 60-90 seconds after administration of thiopental and succinylcholine. This interval was increased to 120 seconds in 2014. Ninety-three patients were included (40 in 2013, and 53 in 2014). Outcome measures were length of seizure, number of re-stimulations, number of ECTs per series and stimulation dosage. Regression model analyses were conducted with entering year of treatment (2013 versus 2014), sex and age as covariates.

### Results

We showed that a lowered frequency of re-stimulation was independently associated with the 2014 treatment regimen. No effect of treatment regimen on duration of seizures as measured clinically or by EEG, on number of treatments per series or on stimulation dosage was observed.

### Conclusions

We found an association between an increased time interval from administration of thiopental and succinylcholine to ECT and a lowered risk of re-stimulations. The current study substantially strengthens the evidence on the benefits of delaying ECT after administration of anaesthetic agent and muscle relaxant.

Keywords:

- 1) Electroconvulsive Therapy
- 2) Mood disorders
- 3) Psychotic disorders
- 4) Anesthetics

## Introduction

Originally, electroconvulsive therapy (ECT) was performed as a brief electrical pulse without concurrent anaesthesia and muscle relaxation, but it has since evolved with multiple types of anaesthetic and muscle relaxants being used (1). Over time, various anaesthetic agents have been evaluated (2,3), originally focusing on barbiturates, their derivatives, e.g. methohexital, and propofol, but with a shifted focus to other agents in the last decade, e.g. ketamine (4). The electrical stimulus dosages required to induce seizures (seizure threshold) is influenced by the ECT regimen employed, but also by age and gender (5–7). Across treatment settings, the time from administration of anaesthetics and muscle relaxants to ECT initiation varies. It is generally assumed that increasing this time interval improves the seizure quality, but the evidence is limited (8). The study by Galvez et al (8) showed that prolonged time since administration of anaesthetics was associated to better seizure quality in patients treated with propofol and succinylcholine. In that study the time from administration of anaesthetics and muscle relaxant to ECT was prolonged as long as possible, making it harder to interpret results and harder to make clinical guideline suggestions to be implemented clinically. Additionally, Sartorius et al (9) have shown that a lighter thiopental anaesthesia leads to an earlier remission, but timing was not included in their study. No further studies have investigated the effects of prolonging time from administration of anaesthetics and muscle relaxant to ECT, as far as the authors are aware.

At Aalborg University Hospital ECT was administered approximately 60 to 90 seconds after administration of succinylcholine (previous treatment regimen) before 2014. However, based on the clinical observation from treating physicians that seizure duration increased in patients who had a longer period from administration of muscle relaxant to ECT, the period between administration of succinylcholine and ECT was increased to 120 seconds (present treatment regimen) by discretion of the head of the ECT department from 2014 onwards. In this setting, the established ECT practice is using brief-pulse stimulus under anaesthetic cover with bilateral electrode placement with initial stimulus dosage determined by the half-age method.

## Aims of the study

We investigated the effect of an increased time interval between the administration of thiopental and succinylcholine on one hand and initiation of the electrical stimulation on the other hand. Our hypothesis was, that that postponing the electrical stimulation would result in longer seizure length, lower number of treatments per series, lower stimulation dose and a reduced need for re-stimulation.

## Materials and Methods

### Design

A retrospective case record-based cohort study comparing two different ECT procedures.

### Study population

Patients received ECT at Aalborg University Hospital, Department of Psychiatry, Region North Jutland, Denmark. Patients aged 18 years or above who had at least one series of ECT between January 1<sup>st</sup>, 2013 and December 31<sup>st</sup>, 2014 were included. We defined index ECT as the first ECT procedure in the first series of treatments (index series) occurring in the study period. Both genders were included, and participants should be at least 18 years of age at index. Only patients initiated on thiopental were included, and change in anaesthetic agent during the index series resulted in censoring from further analysis at that point.

Patients who had received ECT during the previous two years up to index were excluded. Patients receiving maintenance ECT or who received a muscle relaxant other than succinylcholine were excluded.

Data collection was initiated January 2015 and concluded November 2015.

## Procedure

Case records from all patients receiving ECT between January 1<sup>st</sup>, 2013 and December 31<sup>st</sup>, 2014 were evaluated with respect to the study requirements defined here below. Between January 1<sup>st</sup>, 2013 and December 31<sup>st</sup>, 2013 patients were treated according to the previous treatment regimen (ECT initiated 60 to 90 seconds after administration of succinylcholine). In the period January 1<sup>st</sup>, 2014 to December 31<sup>st</sup>, 2014, patients were treated according to the present regimen (ECT initiated 120 seconds after administration of succinylcholine).

The ECT procedure is overseen by a senior consultant, head of the ECT unit, who is responsible for training and supervision of all medical doctors and nurses involved in ECT treatment. The overall treatment team administering ECT is heterogeneous and consists of several smaller teams administering anaesthesia as well as the ECT over the study period. Due to this fact strict guidelines for anaesthesia as well as for ECT have been developed by the head of the ECT unit, to ensure a standardized treatment despite of changes in treatment team over times, and additionally the treatment is often supervised directly by the head of the ECT unit. As a result, no further changes were implemented in the treatment regimens implying that the time period from administration of anaesthetic agent to administration of muscle relaxant was unchanged, that the ventilation procedures were unchanged, that the use of a weight adjusted dose of muscle relaxant and anaesthetic agent were unchanged, as well as the use of the Thymatron-IV ECT machine was unchanged. The two cohorts defined by these two treatment regimens were compared on outcomes as described under ECT outcome measures.

## Outcome measures

### ECT outcome measures

We defined the primary ECT related outcomes as duration of seizures in seconds measured through clinical observation and by EEG. Secondary outcomes were defined as use of re-stimulations, number of ECTs, and



mean energy delivered per treatment during the index series. Re-stimulations were not included in the total number of treatments in the index series.

### Statistical analysis

Initially, we performed descriptive statistics comparing the treatment regimens on various baseline measures. For categorical variables, we used chi-squared tests and for variables of continuous nature, we used Student t-tests. Secondly, we employed regression model analysis with ECT outcome measures as defined earlier, and with treatment regimen, gender and age as covariates. Additionally, we conducted sensitivity analysis with an interaction term between treatment regimen and gender, which was added as covariate, in order to investigate probable moderation effects regarding re-stimulations. Furthermore, we used linear regression for length of seizures (clinical and EEG) and stimulation dosage, logistic regression for risk of re-stimulation and negative binomial regression for number of treatments. Moreover, the regression models with multiple observations per patients were adjusted for within patient dependency applying the clustered sandwich estimator. P-values < 0.05 were considered statistically significant. We did not adjust for multiple comparisons to avoid an increased risk of type II errors and to avoid making data unusable for possible future meta-analyses (10). The statistical analyses were conducted utilizing STATA 14 (11).

### Science ethics

The Danish Data Protection Agency approved use of the data (2008-58-0028). No ethical research committee approval was required as data was obtained retrospectively and anonymized before publication.

## Results

Ninety-three patients out of 153 eligible patients were included in the study population (Figure 1).

A total of 40 patients (14 males and 26 females) were included in the 2013 cohort with a mean age of 57.7 years. On average, the patients received 8.47 ECT procedures during the index series. The mean duration of seizures was 31.27 seconds clinically, and 38.62 seconds on EEG. Ten patients (three males and seven females) received a re-stimulation during their series.

*Please insert Figure 1 approximately here*

Fifty-three patients (17 males and 36 females) were included in the 2014 cohort with a mean age of 54.3 years. On average, the patients received 9.00 ECT procedures during the index series. The mean duration of seizures was 35.75 seconds clinically, and 42.56 seconds on EEG. Seven patients (four males and three females) received re-stimulation during their series.

Thiopental doses were weight adjusted with a mean dose of 285.95 mg in 2013, and a mean dose of 243.41mg in 2014. Diagnosis, demographics and medication use for each cohort are described in Table 1.

*Please insert Table 1 approximately here*

In the regression models we showed that longer length of seizures after ECT, as measured clinically, was independently inversely associated with the higher age with a coefficient of -0.20, whereas treatment regimen and sex were not. Similarly, higher age was inversely associated to longer length of seizures as measured by EEG with a coefficient of -.017. Length of seizure as measured by EEG was not associated to treatment regimen or sex.

*Please insert Table 2 approximately here*

The logistic regression analysis showed an association between being treated according to the present treatment regimen and a lower risk of re-stimulation as compared to the previous regimen with an odds ratio (OR) of 0.23 in an adjusted model as shown in Table 2.

Negative binomial regression showed that there was no correlation between number of treatments and treatment regimen, sex or age as shown in Table 2.

Utilizing linear regression we showed that stimulation dosage was associated with sex, but not with treatment regimen or age, as shown in Table 2. Mean stimulation dosage in 2013 was 151.88 mC, as compared to 143.22 mC in 2014.

## Discussion

In this study two different ECT regimens, in 2013 and 2014, respectively were compared. As hypothesized, we found that the present treatment regimen (2014 regimen) with an increased delay of ECT initiation after administration of succinylcholine was associated with a lower risk of re-stimulation compared to the previous treatment regimen (2013 regimen).

Our finding of an unchanged length of seizure time is in contrast to the finding by Gálvez et al (8) who showed an association between a prolonged time interval between propofol administration and ECT initiation and a better seizure quality as measured by amplitude, regularity, stereotypy and post-ictal suppression in 84 patients. However, the study by Galvez et al (8) was based on a single cohort in which the individual time interval from propofol administration to ECT initiation was determined at the discretion of the clinicians, whereas in our study two standardized time intervals from administration of thiopental and succinylcholine to ECT initiation was compared through the comparison of two cohorts. By this design, we reduced the potential influence of factors other than the time interval on the seizures, making the findings easier to interpret.

Age was independently associated with shorter seizures as measured clinically and by EEG in the current study. This finding supports the previous findings of increased stimulation dosages used with increasing age independent of electrode placement (12–15). Previous studies have also shown an effect of sex on stimulation dosage, with females requiring lower dosages for seizures, a result also supported by our analyses (12,14,16).

Indirect evidence suggests, that time from administration of intravenous anaesthetics to ECT initiation should not be too short to avoid the acute anticonvulsive effect from barbiturates or propofol (17,18). Thus, anaesthetic agents like ketamine or etomidate with less anticonvulsive potency exert no negative influence on seizure quality (17). Additionally, it has been demonstrated that in thiopental anaesthesia, the depth of the anaesthesia correlates negatively with seizure quality suggesting that prolonging the time interval from muscle relaxant and anaesthetic agent administration to ECT initiation could be advantageous (18).

In the present study, we chose to investigate only patients receiving thiopental as anaesthetic agent, and censored patients if they were changed to a different anaesthetic agent, thereby decreasing the inherent problems in controlling for different anaesthetics agents.

The relationship between the time interval from administration of succinylcholine to ECT initiation has never been investigated previously in humans. An animal study compared succinylcholine to anaesthetics showing less decreasing effects on risk of seizures of succinylcholine as compared to pentobarbitone, but no difference as compared to fentanyl/droperidol (19). In a study by Lanier et al (20), dogs administered succinylcholine had increases in cerebral blood flow and intracranial pressure, but it is unknown if there was any effect on seizure activity. Knecht et al (21) showed that succinylcholine resulted in a reduction of fast activity in electroencephalograms in awake dogs, but resulted in a low amplitude dominant activity. Succinylcholine has a short half-life, which would make an effect of prolonging time from succinylcholine administration to ECT initiation plausible. One previous study has found that the seizure duration after ECT utilizing rocuronium as muscle relaxant was longer than the duration when utilizing succinylcholine (22). Due to the current study design, we are unable to entangle any specific effect of prolonging succinylcholine from prolonging thiopental administration to ECT.

Utilizing regression models, we adjusted our analyses to differences between the two cohorts on age at index as well as sex. We did not adjust for differences in psychotropic medication. As shown in table 1, there is a numerical higher proportion of patients being treated with antipsychotics in the 2013 cohort as compared to the 2014 cohort, and a higher proportion of patients being treated with benzodiazepines in the 2014

cohort as compared to the 2013 cohort, although none of these differences reach statistical significance in the univariate analyses. Since antipsychotics have been suggested to increase seizure length (23) and since benzodiazepines decrease the length (24), the distribution of these psychotropics across the cohorts might have biased our results towards the null-hypothesis.

Due to unchanged time period between administration of thiopental and administration of succinylcholine, we are unable to differentiate if the findings of improved ECT outcomes are a result of increasing the time from administration of succinylcholine to ECT initiation, or a result of increasing the time from thiopental to ECT initiation. Further studies are needed to resolve this question.

In the current study patients were mainly diagnosed with affective disorders, and possible effects on psychosis is harder to elucidate. Previous studies have shown an effect of adding ECT to antipsychotic treatment in primary psychosis (25,26), and the effects shown in the current study could most likely also apply to this population.

### **Strength and limitations**

The main strength of the study is the use of a clinical sample treated under routine conditions and the use of broad selection criteria, thereby increasing generalizability of the results to clinical practice. Additionally, the use of a standardized time intervals increases the applicability of study results to clinical practice. By including 93 patients, this study is the largest to date investigating the use of increased time intervals from administration of muscle relaxants and anaesthetics to ECT initiation. The use of ECT is common in Danish Psychiatric University Hospitals (27), and data can most likely be generalized to both university and non-university psychiatric hospitals.

A major limitation is the non-randomized design, making an uneven distribution of confounding variables possible. However, the relatively large samples including the majority of the treated patients in the two calendar years, makes it most likely that there are no major differences among the two cohorts.

In conclusion, we found an association between an increased time interval from administration of thiopental and succinylcholine to ECT and a lowered frequency of re-stimulation. The current study substantially strengthens the evidence on the benefits of delaying ECT after administration of anaesthetic agent and muscle relaxant. A perspective for further research would be to conduct a randomized study comparing the two regimens.

## Figure legend

Figure 1: Flow diagram of participants

## Conflict of Interest and Source of Funding

**RW Licht** has received a grant from GlaxoSmithKline for a clinical trial, received speaker fees from Eli Lilly, Janssen-Cilag, Bristol-Myers Squibb, Pfizer, Astra-Zeneca, Lundbeck, GlaxoSmithKline, Otsuka, Servier, and has acted as advisor for Bristol-Myers Squibb, Astra Zeneca, Janssen-Cilag, Otsuka, Eli Lilly, MSD and Sunovion.

**RE Nielsen** has received research grants from H. Lundbeck for clinical trials, received speaking fees from Bristol-Myers Squibb, Astra Zeneca, Janssen & Cilag, Lundbeck, Servier, Otsuka Pharmaceuticals, Eli Lilly and has acted as advisor to Astra Zeneca, Eli Lilly, Lundbeck, Otsuka Pharmaceuticals, Takeda and Medivir.

For the remaining authors, none was declared.

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