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A retrospective comparison of the effects of propofol and etomidate on stimulus variables and efficacy of electroconvulsive therapy in depressed inpatients

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ABSTRACT

Objective: To compare the effects of propofol and etomidate on the stimulus variables and efficacy of electroconvulsive therapy (ECT) in depressed inpatients.
Method: This retrospective study included 54 inpatients (aged 18–75 years) who met the DSM-IV criteria for major depression and were treated with bilateral ECT. For the first part of the study, the primary outcome was the mean stimulus charge per ECT session. For the second part, the main outcome measure was the proportion of patients achieving full remission.
Results: Propofol-treated patients showed a higher mean stimulus charge (etomidate = 227.58 ± 130.44, propofol = 544.91 ± 237.56, $p < 0.001$) despite the lack of a significant difference in starting threshold doses. The propofol group had shorter mean electroencephalogram (etomidate = 69.41 ± 22.50, propofol = 42.95 ± 22.26, $p < 0.001$) seizure duration and motor (etomidate = 46.11 ± 14.38, propofol = 22.89 ± 7.13, $p < 0.001$) seizure duration and a higher mean number of inadequate seizures (etomidate = 0.12 ± 0.15, propofol = 0.47 ± 0.26, $p < 0.001$). No significant differences were found between the groups for the effects of the anesthetics on the efficacy of ECT.
Limitations: Our study is limited by a retrospective design and the small number of patients treated with propofol restricted the sample size.
Conclusions: Anesthesia with propofol has a significant reducing effect on seizure duration during the course of ECT which results in more inadequate seizures, despite the use of a higher mean stimulus charge. Regarding the possible effect of the anesthetics on ECT, randomized clinical trials with sufficient power to detect differences are warranted.

1. Introduction

Electroconvulsive therapy (ECT) is more effective than both 'sham' ECT and pharmacotherapy in the treatment of patients diagnosed with severe depression (Fink and Taylor, 2007; Kho et al., 2003; UK ECT review Group, 2003). A reduced efficacy of ECT has been shown in patients known with antidepressant pharmacotherapy failure (Heijnen et al., 2010). A longer duration of the index episode is associated with lower remission rates (Dombrovski et al., 2005; Kho et al., 2005; Prudic et al., 2004). There is some evidence for increased efficacy in elderly patients (Gormley et al., 1998; O'Connor et al., 2001; Tew et al., 1999; Wilkinson et al., 1993) and in patients with psychotic major depression (Birkenhager et al., 2003; Pande et al., 1990; Petrides et al., 2001).

Almost all anesthetic agents have anticonvulsant properties because of their effects on the gamma-aminobutyric acid receptors and may, therefore, influence seizure variables and clinical outcome of ECT (Tan and Lee, 2009; Vaidya et al., 2012). Stimulation parameters, such as electrical dosage and electrode placement, are also known to affect response to ECT (Sackeim et al., 1993). Factors affecting the seizure threshold, such as age, sex, concomitant medication with anticonvulsive or proconvulsant properties and electrode placement, could affect both the quality and duration of seizures (Chung, 2002; Sackeim et al., 1991).

There is no clear guideline regarding which anesthetic agent is the most appropriate for ECT. However, propofol is reported to have more anticonvulsant properties compared with methohexital, thiopental and etomidate (Ding and White, 2002; Mitchell et al., 1991). From an anesthetic point of view, propofol is an ultra short-acting anesthetic agent, presumably associated with a rapid recovery, an attenuating effect on the hemodynamic response due to ECT, and less side-effects (Eranti et al., 2009; Patel et al., 2006; Vaidya et al., 2012).

Abbreviations: DSM-IV, Diagnostic and Statistical Manual of Mental, Disorders, fourth edition; ECT, electroconvulsive therapy; HAM-D, Hamilton Rating Scale for Depression; MADRS, Montgomery-Asberg Depression Rating Scale; EEG, electroencephalogram; SPSS, Software package for statistical analysis; mC, milliCoulomb; RCT, Randomized controlled trial; TCA, Tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; SD, standard deviation; df, degrees of freedom; d, Cohen's d; φ, Phi coefficient.

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Etomidate has retained its popularity because of its rapid onset, fast metabolization and recovery, good cardiovascular stability as opposed to propofol, and the best hemodynamic stability among all anesthetic drugs (Abdollahi et al., 2012; Ding and White, 2002; Patel et al., 2006). Etomidate is also associated with a longer seizure duration compared with methohexital, thiopental and propofol (Ding and White, 2002). The adverse effects of etomidate include myoclonus, dystonic reactions, nausea and vomiting (Abdollahi et al., 2012; Griffeth and Mehra, 2007; Patel et al., 2006).

Several studies have compared the effects of etomidate and propofol on stimulus variables during ECT. Most of these had a crossover design, with an equal distribution of baseline characteristics between the two groups (Avramov et al., 1995; Gazdag et al., 2004, 2007; Stadtland et al., 2002; Tan and Lee, 2009). Unfortunately, these studies switched induction agents during the same course of ECT, which is not compatible with a consistent stimulus dose technique since the required dose increases differently for etomidate and propofol during the ECT course. One small randomized controlled trial (RCT) made use of unilateral ECT (Rosa et al., 2008). Only two retrospective studies have examined the effects of etomidate and propofol on the efficacy of ECT (Eranti et al., 2009; Patel et al., 2006). However, these studies did not adjust for several variables that may influence the seizure threshold and efficacy of ECT. All these limitations may have led to difficulties in estimating the effects of the anesthetic agents.

The present study compares the effects of propofol and etomidate on the stimulus variables and efficacy of bilateral ECT in patients diagnosed with major depression. A consistent stimulus dose technique was used and the groups were matched for variables known to affect seizure threshold and efficacy of ECT.

2. Methods

2.1. Research design and patient sample

This retrospective study was performed at the inpatient depression unit of the Department of Psychiatry at the Erasmus Medical Center. The patient sample was restricted to patients aged 18–75 years treated with an inpatient course of ECT, with either propofol or etomidate as anesthetic agent. In this center, etomidate is the most commonly used anesthetic during ECT. A total of 25 patients had received propofol in the context of a completed prospective study (Vukadin et al., 2011). Another 5 patients were switched from etomidate to propofol because they had several prolonged seizures. Furthermore, 2 patients were treated with propofol because of relative contraindications for etomidate. Data for this study were obtained by chart review.

Patients were included for the present study when they met the DSM-IV criteria (American Psychiatric Association, 1994) for major depression and had a baseline score of ≥17 on the 17-item Hamilton Depression Rating Scale (HAM-D) (Bech et al., 1986) before treatment with ECT. Patients treated with unilateral ECT were excluded. Moreover, the post-treatment score on the HAM-D and Montgomery–Asberg Depression Rating Scale (MADRS) (Muller et al., 2000) had to be present for all patients. The five patients who switched from etomidate to propofol because they had several prolonged seizures, were all excluded because they did not meet the DSM-IV criteria for major depression.

Each propofol-treated patient was matched to another patient treated with etomidate, taking into account the age, gender and presence of psychotic features. After individual matching, the groups were compared regarding additional baseline characteristics known to affect the seizure threshold and efficacy of ECT.

Patients who did not complete their intended course of ECT were excluded for the second part of this study which investigated the effects of the anesthetics on the efficacy of ECT. Patients who received both anesthetics during the course of ECT were also excluded for the efficacy part of this study.

2.2. Electroconvulsive therapy

ECT was administered with a brief-pulse (pulse width = 0.5 ms) constant-current Thymatron IV system (Thymatron, Somatics, IL, USA). All patients were treated with bilateral ECT twice weekly. Anesthesia was induced with intravenous etomidate (0.2–0.3 mg/kg) or propofol (1.0–2.0 mg/kg), after premedication with the anticholinergic agent glycopyrolate (0.2 mg). Muscle relaxation was generally achieved with intravenous succinylcholine (1.0 mg/kg). When inadequate seizures occurred at maximum stimulus setting (1008 mC), theophylline was given in order to increase the seizure duration (Leentjens et al., 1996).

The stimulus dose-titration method (Sackeim et al., 1997) was used to determine the seizure threshold during the first ECT session. The stimulus dosage was set at 50% above the threshold dose during the second session. Both motor seizure duration and electroencephalogram (EEG) seizure duration were recorded during ECT. Motor seizure duration was timed visibly using the cuff method (van den Broek et al., 2004). EEG seizure duration is based on the Thymatron machine assessment of duration. During the course of ECT, stimulus dosage settings were adjusted upward to maintain seizure duration of at least 25 s as measured with the cuff method, in order to avoid the occurrence of seizures with a motor duration of ≤20 s. ECT was continued until patients achieved remission or showed no further improvement over three consecutive treatments. A minimum of 10 bilateral treatments was required before evaluation as a nonresponder.

2.3. Outcome measures

The present study compared the effects of etomidate and propofol on the stimulus variables and efficacy of ECT. The study examined potential differences concerning the starting threshold dose and mean stimulus charge per session. The stimulus charge will often increase during the course of ECT. Therefore, results could be affected in case of a different length of the ECT course in the groups. The results for the mean stimulus charge were corrected for the number of ECT sessions. This study compared the mean motor seizure duration and EEG seizure duration per session. Mean values per session were defined as the total charge or seizure duration of all ECT sessions together divided by the number of sessions during the course. In case of restimulation, only the last stimulation was used. The mean number of inadequate seizures per attempt and the number of patients who received theophylline addition were also examined. Inadequate seizures were defined as no seizure or motor seizure duration of ≤20 s.

The second part of this study examined the effects of the anesthetic agents on the percentage of response or remission, and the number of ECT sessions required to achieve response or remission. Remission was determined by a score of ≤8 on the MADRS. The definition of response was a decrease of at least 50% on the MADRS. The mean reduction of HAM-D and MADRS scores during ECT was also recorded. Additional subgroup analyses without patients who received theophylline were also performed regarding the percentage of response and remission, and HAM-D reduction.

2.4. Statistical analyses

Differences between the anesthetic agents were tested with Chi-square tests and two-sample t-tests (or the Mann–Whitney U test where appropriate). The Chi-square statistic with Yates's correction for continuity was calculated for comparison of two categories. The Fisher's exact test was used in the presence of table cells with an expected count less than five. Analysis of covariance was used to provide a statistical control for the effect of the length of the ECT course on the mean stimulus charge per session. Statistical significance was set at 5% level, two-tailed. Analyses were performed using SPSS version 17.0.