Eur Arch Psychiatry Clin Neurosci (2016) 266:719–724
DOI 10.1007/s00406-016-0690-9

ORIGINAL PAPER

Does remifentanil improve ECT seizure quality?

Verònica Gálvez[1,2] · Phern-Chern Tor[3] · Adriana Bassa[1,2,4] · Dusan Hadzi-Pavlovic[1,2] · Ross MacPherson[5,6] · Mincho Marroquin-Harris[5] · Colleen K. Loo[1,2,7]

Received: 29 November 2015 / Accepted: 6 February 2016 / Published online: 1 April 2016

Abstract Studies have reported that co-adjuvant remifentanil can enhance electroconvulsive therapy (ECT) seizure quality, putatively by allowing a reduction in the dosage of the main anaesthetic agents, as the latter have anticonvulsant properties. However, whether remifentanil also has direct effects on ECT seizure quality, and by implication, treatment efficacy, is unknown. This is the first study examining the effect of adjuvant remifentanil on ECT seizure quality when the dose of conventional anaesthesia remained unchanged. A total of 96 ECT sessions (from 36 patients) were retrospectively analysed. Subjects received ECT with and without remifentanil (1 μg/kg), while the dose of thiopentone (3–5 mg/kg) or propofol (1–2 mg/kg) was unchanged. Seizure quality indices (time to slow wave activity or TSLOW, amplitude, regularity, stereotypy, post-ictal suppression) and duration were assessed through a structured rating scale by a single trained blinded rater. Linear mixed-effects models with random subject effects analysed the effect of remifentanil on seizure parameters, controlling for other variables that can affect seizure quality or duration. Remifentanil was given in 47.9 % of the ECT sessions. Co-adjuvant remifentanil had no effects on any of the seizure quality parameters analysed [TSLOW ($E = -0.21$, $p > 0.1$), amplitude ($E = 0.08$, $p > 0.5$), regularity ($E = -0.05$, $p > 0.5$), stereotypy ($E = -0.02$, $p > 0.5$), suppression ($E = -0.3$, $p > 0.05$)] or on seizure duration ($E = -0.25$, $p > 0.1$). While adjuvant remifentanil may be a useful strategy for reducing anaesthetic dosage in ECT, present evidence suggests that remifentanil does not have intrinsic properties that enhance ECT seizures.

Keywords Electroconvulsive therapy · Remifentanil · Seizure · EEG · Duration · Anaesthesia

Introduction

Remifentanil is an ultrashort acting opioid frequently used in sedation, analgesia and supplementation of general anaesthesia due to its rapid onset and the short duration of its effects [1]. Remifentanil is also being used in electroconvulsive therapy (ECT) settings, mainly as a co-adjuvant for conventional anaesthetics, although there are limited data regarding its effects on ECT outcomes (for a review see [2]).

At present, it is unclear whether remifentanil has any direct, intrinsic properties in enhancing ECT-induced seizures, or is mainly useful for enabling dose reduction of conventional anaesthetics. Most of the studies in this topic have examined the effects of remifentanil on seizure duration, when used as a co-adjuvant anaesthetic [3–10]. Seizure duration was reported to be longer when remifentanil was used with reduced doses of the conventional

✉ Colleen K. Loo
colleen.loo@unsw.edu.au

1 School of Psychiatry, University of New South Wales (UNSW), Randwick, NSW, Australia

2 Black Dog Institute, Randwick, NSW, Australia

3 Department of General Psychiatry, Institute of Mental Health, Singapore, Singapore

4 Department of Psychiatry, Bellvitge University Hospital, L'Hospitalet de Llobregat, Barcelona, Spain

5 Department of Anaesthesia and Pain Management, Royal North Shore Hospital, Sydney, NSW, Australia

6 Department of Anaesthesia, The Northside Clinic, Sydney, NSW, Australia

7 Department of Psychiatry, St George Hospital, Kogarah, NSW, Australia

anaesthetics, but not if the doses of the anaesthetics were maintained [11–14]. Thus, this suggests that remifentanil may augment seizure duration by allowing a *reduction* in the dose of the main anaesthetic agent [2]. However, seizure quality is a more relevant outcome than seizure duration. Seizure quality measures are important in ECT because they can be useful on guiding therapeutic decisions over the ECT course [15, 16]. Typically, when the quality of the seizure declines, this may be indicative of an increase in seizure threshold (ST) [15]. In ECT clinical practice, to compensate for the increase in ST represented by a decrease in seizure quality, the stimulus dose is increased with the aim of maintaining an acceptable quality seizure. This is because several studies have reported higher quality seizures (higher spike and wave amplitudes, shorter latency to the slow wave phase and greater post-ictal suppression) to be associated with better antidepressant outcomes [15, 17–21]. There are however several individual and treatment variables that can also affect the quality of the seizures, independently of treatment outcomes. Electroencephalographic (EEG) seizure expression can vary substantially between individuals [22] and also tends to decline over an ECT course on an individual patient basis. For example, higher quality seizures with greater amplitude and suppression have been correlated with younger individuals [16, 18], higher stimulus intensities [18], bitemporal electrode placements [19, 23], earlier treatments in the ECT course [24, 25], more days in between ECT treatments [25] and longer anaesthetic-ECT times [25]. Thus, it is important to consider all these factors when analysing seizure quality.

Only two studies have investigated the effects of remifentanil on seizure quality indices when remifentanil was added to the main anaesthetic agent. In particular, increases in seizure suppression [7] and mid-ictal EEG amplitude and coherence [5] were found when remifentanil was added to propofol anaesthesia. However, in both of these studies the dose of propofol was diminished when remifentanil was used. This suggests that, as in seizure duration, seizure quality improvement could be due to the *reduction* in the dose of the main anaesthetic agent, rather than to the *addition* of remifentanil itself, as most of the intravenous anaesthetic agents used for ECT possess dose-related anticonvulsant properties [26].

To date, no study has examined the impact of remifentanil on EEG quality independently of dose reduction of the main anaesthetic agent. The present study sought to clarify whether there is an independent effect of remifentanil on ECT seizure quality, apart from the "anaesthetic-sparing effect" produced by the diminution of dose of the other anaesthetics. We hypothesised that adjuvant remifentanil would have no significant effects on ECT seizure quality, when the dose of conventional anaesthetics remained unchanged and after controlling for other variables that can also affect seizure quality.

Materials and methods

Sample and study design

EEG, clinical, demographic and ECT treatment data were collected from ECT sessions at Northside Clinic Hospital (Sydney, Australia) from September 2007 to May 2013. The study was approved by the Ramsay Hospital Research Ethics Committee (approval number 175). Inclusion criteria for this study were: age $\geq$18 years/old and had received an acute course of ECT in which remifentanil was given in some but not all treatment sessions. If patients received more than one ECT course during the study period, only data from the first ECT course were analysed. Within each patient's ECT treatment course, ECT sessions and corresponding EEGs were selected for analysis if they were given with identical ECT treatment parameters (electrode placement, pulse width) and the same anaesthetic agent (i.e. either thiopentone or propofol), but varied in whether remifentanil was used. Titration sessions were excluded.

Some of the data reported in this paper overlap with data analysed and reported in MacPherson et al. [27], but the analysis approach and results are completely independent. The MacPherson paper investigated effects separating analyses for different anaesthetic agents, used *t* test comparisons which did not control for ECT treatment parameters and did not account for the substantive effect of inter-individual variability on EEG seizure quality.

ECT procedures

ECT was administered using a MECTA Spectrum 5000Q device (Mecta Corp., Lake Oswego, OR, USA). Right unilateral (RUL), bitemporal (BT) and bifrontal (BF) electrode placements were used. Pulse width was brief (0.5–1 ms) or ultrabrief ($\leq$0.3 ms). Seizure threshold (ST) was established by a titration method on the first ECT session, and ECT dose at consecutive ECT treatments was given at: 5 $\times$ ST for unilateral (UL) brief ECT, 6 $\times$ ST for UL ultrabrief ECT, 1.5 $\times$ ST for bilateral (BL) brief ECT and 3 $\times$ ST for BL ultrabrief. The first supra-threshold treatment was given in the second ECT session. ECT treatments were generally administered three times a week.

Anaesthetic induction was with thiopentone (2.5–5 mg/kg) or propofol (1–2 mg/kg), with succinylcholine (0.5–1 mg/kg) as a muscle relaxant. The same anaesthetic agent (propofol or thiopentone) was used throughout the ECT sessions selected for analysis from each patient's

treatment course. If used, remifentanil (1 μg/kg) was given immediately after the induction agent (propofol or thiopentone) without any change in the dose of the main anaesthetic. The decision to use remifentanil or not was at the discretion of the anaesthetist. While all anaesthetists agreed that the dose of propofol or thiopentone should be as low as possible (given their anticonvulsant effects), some anaesthetists used co-adjuvant remifentanil to reduce the risk of awareness when a low dose of propofol or thiopentone was used, whereas other anaesthetists considered it was not necessary to use remifentanil when giving the same low dose of propofol or thiopentone.

Data were collected on the following ECT treatment variables: anaesthesia used (thiopentone vs. propofol), use of remifentanil (yes/no), ECT electrode placement (RUL, BF, BT), ECT pulse width (brief vs. ultrabrief), charge (mC), ECT treatment number (order of the treatment in the ECT course) and days between ECT treatments. Thiopentone dose was transformed to propofol equivalents (in mg) for subsequent analysis, based on the hypnotic potency ratio: 2 mg thiopentone = 1 mg propofol [28, 29]. Pulse width was grouped into brief (0.5–1 ms) or ultrabrief (≤0.3 ms) for the analysis.

EEG procedures

EEG recordings were performed through two frontal-mastoid EEG channels. Seizure quality indices (TSLOW or time to slow wave activity ≤5 Hz), amplitude (in mm), regularity [e.g. intensity or morphology of the seizure (0–6), stereotypy (or global seizure patterning, 0–3) and post-ictal suppression (0–3)] as well as seizure duration (in seconds) were assessed through a structured rating scale [30], by a single trained rater (PCT), who showed inter-rater reliability with CL and VG (ICC ≥ 0.8 for each item of the rating scale) and was blinded to all clinical, demographic and ECT data (including use of remifentanil).

Statistical analysis

EEG outcome variables (TSLOW, amplitude, regularity, stereotypy, post-ictal suppression and duration) were normalised using Box-Cox transformation (SPSS, v.21). Linear mixed-effects models with subject as a random effect were used to analyse the effect of remifentanil on seizure quality indices and seizure duration, i.e. modelling correlated observations pertaining to the same individuals. A separate mixed-effects model was run for each dependent variable (TSLOW, amplitude, regularity, stereotypy, post-ictal suppression and duration), controlling for variables that could potentially have an effect on seizure expression: anaesthesia type (use of propofol or thiopentone) [31], anaesthesia dose (propofol mg equivalents) [17], electrode placement (RUL, BF, BT) [19, 23], pulse width (brief/ultrabrief), age (years) [17, 18, 25, 32, 33], ECT charge (mC) [16, 18, 19], ECT session number [24, 25] and days between ECT [25]. SPSS (v.21) was used for analysis.

Results

A total of 99 EEGs were obtained. From these, three EEGs were excluded due to artefacts. In total, 96 EEG recordings were analysed from 36 subjects. Remifentanil was given in 47.9 % of the ECT sessions. Equipotent dose of anaesthesia (in mg of propofol) did not differ between ECT sessions with or without remifentanil [mean equipotent dose of anaesthesia with remifentanil: 94.24 mg (SD 22.98), mean equipotent dose of anaesthesia without remifentanil: 89.90 mg (17.84), $p > 0.1$]. Table 1 shows descriptive statistics of the sample by subjects and ECT sessions.

Effects of remifentanil on seizure quality and duration

The mixed-effects analyses showed remifentanil had no significant effects on any of the seizure quality parameters analysed. Results were non-significant for TSLOW [$E = -0.21$, $p > 0.1$], amplitude [$E = 0.08$, $p > 0.5$], regularity [$E = -0.05$, $p > 0.5$], stereotypy [$E = -0.02$, $p > 0.5$] and seizure duration [$E = -0.25$, $p > 0.1$], while there was a trend for lower post-ictal suppression when remifentanil was used ($E = -0.3$, $p = 0.08$).

Effects of other variables on seizure quality and duration

Of the other variables tested, only age had significant effects on seizure quality. Older age impacted negatively on seizure amplitude ($E = -0.03$, $p < 0.01$), regularity ($E = -0.23$, $p < 0.05$) and post-ictal suppression ($E = -0.24$, $p < 0.05$). In contrast to RUL placements, BF ($E = -1.07$, $p < 0.05$) and BT placements ($E = -1.34$, $p < 0.05$) produced significantly shorter seizures. Compared to brief pulse (0.5–1 ms), ultrabrief pulse ECT (≤0.3 ms) produced significantly shorter seizures ($E = -1.17$, $p < 0.05$).

Discussion

This is the first study examining the effects of remifentanil on seizure quality, when given without alteration in the dose of the main anaesthetic agent. Present results suggested that the addition of remifentanil, per se, without reducing the dose of the main anaesthetic does not confer

Table 1 Descriptive statistics of the sample by subjects and by ECT sessions

Variable	Mean (%)	SD
By subjects	$N = 36$	
Age (years)	51.5	16.6
Gender (male)	50 %	
Variable	Mean (%)	SD
By EEG (ECT session)	$N = 96$	
Remifentanil (Y/N)	47.9 %	
Anaesthetic type		
Propofol	79.2 %	
Thiopentone	20.8 %	
Anaesthesia dose (propofol mg equivalents)	92.0	20.5
ECT charge (mC)	572.5	348.4
Electrode placement		
Right unilateral (RUL)	58.3 %	
Bitemporal (BT)	10.4 %	
Bifrontal (BF)	31.3 %	
Pulse width		
Brief (0.5–1 ms)	50 %	
Ultrabrief (≤0.3 ms)	50 %	
Time between ECT sessions (days)	3.3	2.0

Y yes, *N* no, *mg* milligrams, *mC* millicoulombs, *ms* milliseconds

an advantage for ECT seizure quality or duration. This reinforces the hypothesis that prior positive findings with remifentanil on seizure suppression [7], seizure intensity [5] and seizure duration [3–10] are more likely explained by the reduction in dosage of the main anaesthetic agent when remifentanil was used, than to intrinsic effects of remifentanil on the seizure. The trend level finding of lower post-ictal suppression in sessions involving remifentanil should be interpreted with caution, given its failure to reach significance and the small sample size.

Indeed, it is unclear from the existent human and animal literature whether opioids, in general, and remifentanil in particular possess any anticonvulsant or pro-convulsant properties, or both, depending on the dosage used [34, 35]. Dosages used in this study were co-adjuvant and hence in the lower range (1 μg/kg). Initial animal pharmacokinetic studies using remifentanil suggested that it produced suppression of the EEG activity [36]. However, animal studies using considerably higher dosages (20–60 μg/kg) suggested that EEG activation (low frequency rhythmic, high-voltage spikes) during remifentanil infusion was generally increased with increasing doses [37]. Two case reports using remifentanil alone [38] and with propofol [39] reported spontaneous seizure-like activity in humans, suggesting a pro-convulsant effect. However, EEG data were not obtained at the time of the seizure-like event or closely after in any of these cases. A large study including 127 subjects anaesthetised with opioids other than remifentanil did not find evidence for opioid-induced seizures. In this study, no seizure activity was reported through EEG monitoring. However, muscle rigidity was found in 46 cases, with no alterations in EEG recordings. This study thus suggests that muscle rigidity is a common phenomenon when opioids are used and that it could be confounded as seizure activity in the absence of EEG recording [40].

It is also possible that the effects of remifentanil on ECT seizures could further vary depending on whether remifentanil is used alone as an anaesthetic or as a co-adjuvant of other anaesthetics. Marked reductions in ST have been reported with the use of remifentanil as a sole anaesthetic (4–8 μg/kg) compared to methohexital [41]. In this study, 24 subjects who did not have adequate seizures with methohexital at maximum ECT device dose settings (576 mC) were switched to remifentanil as an alternative anaesthetic strategy. Seizure threshold with remifentanil was significantly lower compared to methohexital (mean ST for methohexital: 174.8 mC, mean ST for remifentanil: 114.7 mC). Also, the increase in ST between the first and the last remifentanil ECT treatments was not significant, in contrast to the significant increase found between the first and the last methohexital ECT treatments. These results can be interpreted in two ways: (1) remifentanil does not appear to have anticonvulsant properties and therefore does not have an effect on ST or (2) remifentanil can have pro-convulsant properties when used at higher dosages as a sole anaesthetic, having a positive effect in reducing ST.

Secondary findings of this study support prior research suggesting that seizure quality can be altered by other factors. As previously reported [18, 23, 25, 32, 33], older age was found to be associated with a decrease in the quality of the ECT seizures in our sample.

Strengths of this study include the careful detailed analyses that controlled for other important factors known to affect seizure quality and utilised a repeated measures design, accounting for repeated measures pertaining to the same individual. However, several limitations need to be acknowledged. Analysis was based on clinically collected data, rather than in a randomised trial design. Sample size was limited, with only 36 subjects participating in the study. EEG measures were performed only through two EEG channels. Other factors that might have impacted EEG seizure quality, such as anaesthetic-ECT timing [25], other aspects of the anaesthesia technique and concurrent medications, were not controlled for in this study. Emerging evidence suggests, however, that concurrent medication might have no influence on seizure adequacy outcomes [25, 33]. As all patients in this study received some treatments with remifentanil, and some without, and clinical efficacy

outcome measures were not available, this study was not able to assess whether the use of remifentanil affected clinical ECT efficacy. A prospective, parallel design trial in which some patients are assigned to receive ECT with remifentanil, and some without, would be required to address this question. Lastly, the relationship between seizure quality and efficacy outcomes is complex, with some studies only reporting a modest association [23]. Thus, the potential of EEG markers to predict treatment adequacy might be limited.

In conclusion, while co-adjuvant remifentanil use might be a useful strategy to minimise the dose of conventional anaesthetic agents in ECT, it does not appear to have intrinsic ECT seizure-enhancing properties. When remifentanil was added at co-adjuvant doses for ECT anaesthesia, without the reduction in dose of conventional intravenous anaesthetics, there was no improvement in seizure quality or change in seizure duration. Implications for clinical practice are that the addition of co-adjuvant remifentanil is not useful for enhancing ECT-induced seizures, unless it is accompanied by a reduction in the dose of the main anaesthetic agent.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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