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Review Article

Anaesthesia for electroconvulsive therapy – new tricks for old drugs: a systematic review

Stripp TK, Jorgensen MB, Olsen NV. Anaesthesia for electroconvulsive therapy – new tricks for old drugs: a systematic review.

Objective: The objective of this review is to investigate existing literature in order to delineate whether the use of anaesthesia and timing of seizure induction in a new and optimised way may improve the efficacy of electroconvulsive therapy (ECT).
Methods: PubMed/MEDLINE was searched for existing literature, last search on 24 June 2015. Relevant clinical studies on human subjects involving choice of anaesthetic, ventilation and bispectral index (BIS) monitoring in the ECT setting were considered. The references of relevant studies were likewise considered.
Results: Propofol yields the shortest seizures, etomidate and ketamine the longest. Etomidate and ketamine + propofol 1 : 1 seems to yield the seizures with best quality. Seizure quality is improved when induction of ECT is delayed until the effect of the anaesthetic has waned – possibly monitored with BIS values. Manual hyperventilation with 100% O_2 may increase the pO_2/pCO_2-ratio, which may be correlated with better seizure quality.
Conclusion: Etomidate or a 1 : 1 ketamine and propofol combination may be the best method to achieve general anaesthesia in the ECT setting. There is a need for large randomised prospective studies comparing the effect of methohexital, thiopental, propofol, ketamine, propofol + ketamine 1 : 1 and etomidate in the ECT treatment of major depressed patients. These studies should investigate safety and side effects, and most importantly have antidepressant efficacy and cognitive side effects as outcome measures instead of seizure quality.

Tobias Kvist Stripp[1], Martin Balslev Jorgensen[2], Niels Vidiendal Olsen[1,3]

[1]Department of Neuroscience and Pharmacology, The Health Faculty, University of Copenhagen, Copenhagen, Denmark; [2]Psychiatric Centre Copenhagen, University Hospital of Copenhagen, Copenhagen, Denmark; and [3]Department of Neuroanaesthesia, The Neuroscience Centre, University Hospital of Copenhagen (Rigshospitalet), Copenhagen, Denmark

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Tobias K Stripp, Department of Neuroscience and Pharmacology, The Health Faculty, University of Copenhagen, 3B Blegdamsvej, DK-2200 Copenhagen, Denmark.
Tel: +45 22 42 25 80;
Fax: +45 35 45 80 32
E-mail: tkstripp@gmail.com

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Summations

- Etomidate or a 1 : 1 combination of propofol and ketamine seems to provide longer and better seizures in the electroconvulsive therapy (ECT) setting.
- Bispectral index (BIS) value-guided timing of seizure induction may result in longer seizure durations.
- Manual hyperventilation may result in better seizures.

Considerations

- The effect of hyperventilation may be due to a longer period before seizure induction resulting in shallower anaesthesia (or higher BIS).

- The material available to this qualitative review is mostly retrospective resulting in compromised scientific quality.
- Many studies cited investigates the topic with outcome measures such as 'seizure duration' which is not equal to 'antidepressant effect'.

Introduction

Major depressive disorder is affecting millions of people worldwide with a massive impact on global well-being and health (1). Antidepressant drugs and psychotherapy are the first-line treatments. However, a large group of patients (around 30%) fail to respond to antidepressants (2–4), and in these patients as well as in patients with the most severe depression ECT is a treatment option. Although the mechanism of ECT is not well understood, it is highly efficacious in severe major depression with melancholic or psychotic features. However, there are side effects such as cognitive dysfunction, especially retrograde and anterograde amnesia (5).

At the moment, there is a wide variation between ECT practices (6,7). Recent studies suggest that the choice of anaesthetic agent is important to ECT practice and thus a review of existing literature regarding this issue is needed. As the dosing of the electric charge is adjusted according to the quality of the seizure, and the side effect largely is determined by the dosing, it is of great importance to consider the impact of the anaesthesia on the seizure. That is, if the anaesthetic procedure inhibits the seizure, in practise the electric charge is heightened leading to increased frequency of cognitive side effects (8).

To examine the influence of anaesthetic agents in ECT, we reviewed retrospective and prospective studies comparing methohexital, thiopental, ketamine, propofol and etomidate anaesthesia in the ECT setting and their different impact on seizure quality and antidepressant efficacy of the ECT in primarily major depressed patients. We reviewed ventilation methods by retrospective studies assessing the impact of pO_2 and pCO_2 on seizure quality in patients undergoing ECT. Furthermore, we searched for the effect of BIS monitor-guided seizure induction in retrospective and prospective studies examining its effect on seizure quality in the ECT treatment of depressed patients.

Aims of the study

The aims of this study was to investigate the effect of different ways of anaesthesia in the ECT setting and their impact on seizure quality. We examined three parameters; the anaesthetic agent used, the ventilation procedure and the effect of using BIS monitoring as guide for seizure induction.

Methods

The search for literature was performed using the PubMed/MEDLINE database for journal articles up to 24 June 2015. The search terms were as follows: ('Electroconvulsive Therapy'[Mesh]) AND 'Hyperventilation'[Mesh]; ('Electroconvulsive Therapy'[Mesh]) AND 'Consciousness Monitors'[Mesh]; ('Electroconvulsive Therapy'[Mesh]) AND 'remifentanil'[Supplementary Concept]; ('Electroconvulsive Therapy'[Mesh]) AND 'thiopental'[Mesh]; ('Electroconvulsive Therapy'[Mesh]) AND 'propofol'[Mesh]; ('Electroconvulsive Therapy'[Mesh]) AND 'methohexital'[Mesh]; ('Electroconvulsive Therapy'[Mesh]) AND 'etomidate'[Mesh]; ('Electroconvulsive Therapy'[Mesh]) AND 'ketamine'[Mesh]. All relevant clinical studies on human subjects involving choice of anaesthetic, ventilation or BIS monitoring in the ECT setting were considered. The references of relevant studies were likewise considered. Studies were not considered if they were only published in abstract form, if they were done in animals or if published in languages other than English (Fig. 1).

Results

The profile of the anaesthetic induction agent should be examined particularly for use in ECT and its possible interaction with the effect of the ECT. Seizure quality is associated with antidepressant efficacy (9–11) and is usually estimated in studies with different parameters: (1) seizure duration; (2) the degree of central inhibition (9,12,13); (3) the mid-ictal amplitude (14); (4) coherence (11,15); and (5) maximal ictal heart rate (10,16).

It is important to bear in mind that seizure quality and antidepressant efficacy is not the same outcome. Despite of this, seizure quality is often used as approximation for outcome of ECT treatment. The anaesthetic has a great impact on many of the parameters measured in seizure quality, and thus it is important to identify the optimal anaesthetic (17,18) (Table 1).

Methohexital

Methohexital is a barbiturate derivative. It is short acting with a rapid onset of action. It potentiates the ionotropic gamma-aminobyturic acid (GABA)-receptor by prolonging the opening time of the channel (19), thus it has some anticonvulsant

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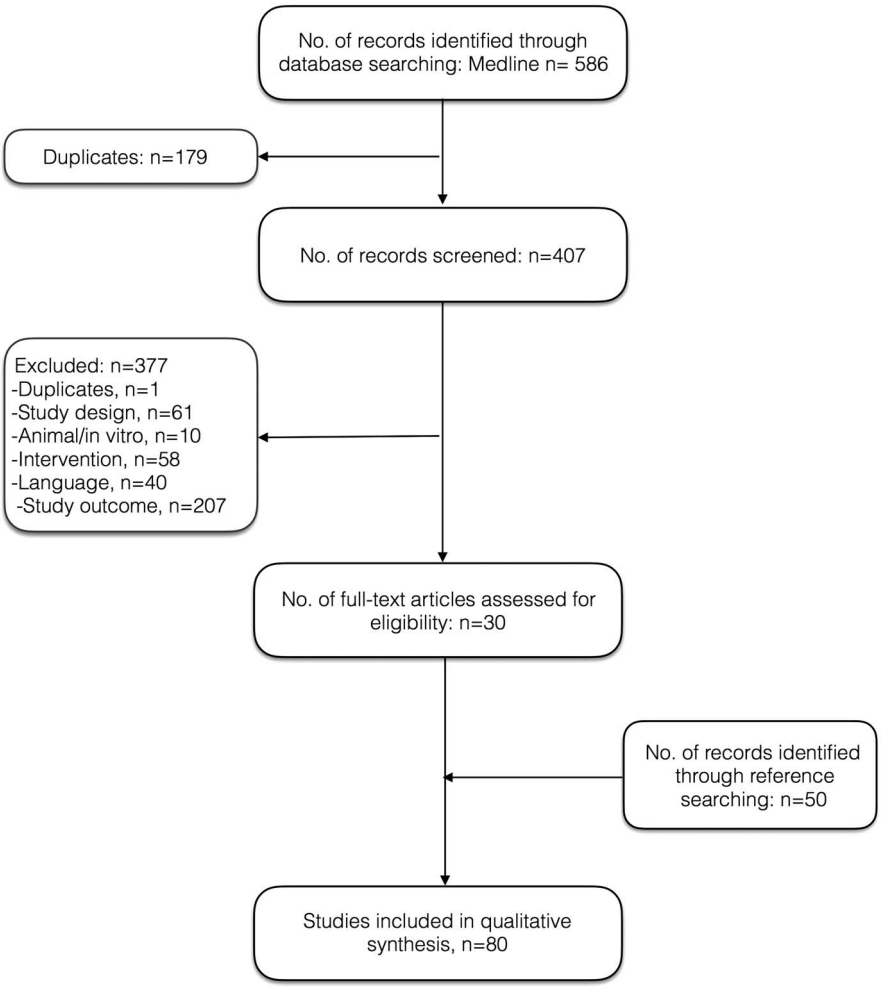

Fig. 1. PRISMA flow chart

Table 1. Qualities of the ideal electroconvulsive therapy (ECT) anaesthetic

Induction	Rapid and smooth induction, painless
Anticonvulsion	Minimal or no antagonistic effect on seizure activity
Duration of action	Short duration of action with fast recovery
Haemodynamics	Haemodynamically stable
Pharmacodynamic	Synergistic or additive effect in relation to the ECT effect

properties (20). In a randomised cross-over study it yielded longer seizures than propofol with worse haemodynamic stability (21). When compared with etomidate in a retrospective study, methohexital yields more cardiac side effects, like bradycardia and cardiac arrhythmia (22). Methohexital has been widely used and does probably still have a place in an ECT anaesthesia regimen.

Thiopental

Thiopental is like methohexital a barbiturate derivative that targets the GABAergic systems of the brain and has some anticonvulsant properties (20). Thiopental has been widely used in the ECT setting as well and was in a randomised blinded study found to yield longer seizures than propofol (8). When compared with etomidate in a randomised double-blinded study, less antidepressive efficacy was found with thiopental (23), and etomidate yielded longer seizure durations when compared with thiopental in a retrospective study (24). Randomised studies find thiopental to yield longer seizures than propofol (8).

Propofol

The mechanism of propofol is mediated through GABA-receptor potentiation and Na^+-channel blockade (25,26), promoting central inhibition and acting as an anticonvulsant. Thus, a higher voltage dose is necessary to achieve adequate seizures in the ECT setting (20). When compared with ketamine, thiopental, methohexital and etomidate in both randomised blinded and retrospective studies, propofol is associated with shorter

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seizure durations (8,21,27,28), more missed seizures and significantly more electrical current is required to treat (29,30). In prospective randomised studies propofol provides a better recovery and haemodynamic profile than the other agents (21,31,32). In regards to the clinical effect of ECT, propofol has been shown to be associated with better or faster outcome than thiopental in prospective randomised studies (8,33). This perhaps at the price of more cognitive side effects due to the strategy of increasing the dose with decreased seizure quality (8). Moreover, propofol had worse outcome than etomidate in two retrospective studies (34,35). Based on both prospective and retrospective studies propofol yields the shortest seizures due to its anticonvulsant properties (8).

Ketamine

Ketamine is a selective *N*-methyl-D-aspartate (NMDA) receptor antagonist (36). Ketamine may be used in terminating drug-resistant, refractory status epilepticus but has no anticonvulsive properties in the ECT setting (37–39).

Sub-anaesthetic doses. The agonist for the NMDA receptor is the neuronal excitatory amino acid glutamate (40), and targeting the glutamate system for antidepressant therapy is a novel and promising approach in the search for a new and rapidly effective antidepressant drug (41). Based on a randomised controlled trial, Berman et al. (42) reported that ketamine in sub-anaesthetic doses produced a rapid, robust and long-lasting antidepressant effect. These results have been replicated in other studies (43–53). In a randomised trial some had success in achieving remission in treatment-resistant depressive patients with the sole use of sub-anaesthetic doses of ketamine (53). In a prospective randomised study, antidepressant effect with ketamine was achieved in patients who had failed to respond to ECT (54). Ketamine has been shown to improve depression rapidly. In addition to NMDA antagonism, evidence for several mechanisms of action have been discovered including altering of intracellular signalling pathways and modification of protein synthesis of mammalian target of rapamycin and brain-derived neurotrophic factor (55–59).

In the ECT setting. In a randomised double-blinded prospective study, ketamine, propofol and ketamine + propofol in a 1 : 1 solution was compared. A greater antidepressant efficacy as well as longer seizures was found in the ketamine and propofol + ketamine groups – with more side effects in the group solely receiving ketamine (60). Two other prospective studies have shown consistent results with highest seizure quality in the ketamine and propofol + ketamine groups – with more side effects in the group solely receiving ketamine (61,62). Recently in a retrospective study of 3239 ECT treatments, etomidate and ketamine anaesthesia were reported to be associated with higher quality seizures than those achieved with propofol and thiopental anaesthesia (63). Seizures were longer with etomidate and ketamine, with ketamine favourable in regards to central inhibition (63). A retrospective study found S-ketamine to be associated with lower charge required to treat compared with thiopental (64). The main issue with ketamine is its side effect profile and cardiovascular stress although it seems that the dissociative symptoms are absent with an anaesthetic dose (65). Compared with thiopental in a retrospective study, ketamine provided better Hamilton depression rating scores and mini-mental state examination scores, faster reorientation time and fewer numbers of ECT required (66). It is still arguable whether ketamine as sole anaesthetic is safe and tolerated, but a 1 : 1 combination with propofol seems very promising, supported by three prospective randomised studies.

Etomidate

Etomidate is a short-acting anaesthetic modulator at the GABA-receptor (67). The favourable haemodynamic profile of etomidate makes it a good choice for anaesthesia in the ECT setting (68). The adrenal medullar suppression of etomidate was tested comparing serum cortisol and adrenocorticotropic hormone levels after repeated ECT treatments with either propofol or etomidate as the anaesthetic agent (69). The study showed slightly depressed levels of cortisol as well as adrenocorticotropic hormone in the etomidate group but levels were still in the normal range and returned to normal baseline values before the next ECT (69), showing that etomidate is safe (70). A recent meta-analysis shows etomidate to be favourable to propofol and thiopental in terms of seizure duration and to methohexital in terms of side effects (22,71). Thus, etomidate may be the drug of choice for ECT anaesthesia. Supported by a large meta-analysis comparing it with propofol, thiopental and methohexital it yields longer seizures (71) and should perhaps be considered before the use of other agents.

Remifentanil

Remifentanil is an opioid capable of inducing general anaesthesia. The use of remifentanil allows a smaller dose of the primary anaesthetic (72). A systematic review suggested that the combination of propofol

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Table 2. Properties of different anaesthetics in the electroconvulsive therapy setting

	Dose	Anticonvulsive properties	Seizure duration	Common side effects
Methohexital	1 mg/kg	++	Intermediate	Nausea, hypotension
Thiopental	2 mg/kg	++	Intermediate	Nausea, hypotension
Propofol	1.5 mg/kg	+++	Short	Injection pain, nausea, vomiting, hypotension
Ketamine	0.8 mg/kg	–	Long	Dissociative symptoms, hallucinations, nausea, vomiting, hypertension
Propofol (P) + ketamine (K)	1.5 mg/kg P + 0.8 mg/kg K	++	Intermediate	Decreased ketaminergic side effects
Etomidate	0.2–0.3 mg/kg	+	Long	Adrenal suppression

with the opioids remifentanil or alfentanil may prolong seizure durations (73). In a prospective randomised study, a low dose of remifentanil (1.0–1.5 µg/kg) significantly reduced myoclonic movements following etomidate injections (74). Remifentanil should probably not be used as the sole anaesthetic-inducing agent, but seems useful as an additive to the anaesthetic when the seizure needs to be prolonged (Table 2).

ECT and BIS

As the intravenous anaesthetic agents have different anticonvulsant properties in the central nervous system, they have different impact on the progress of the induced seizure in the ECT setting (20). BIS value algorithms are based on normal brain function and thus is questionable in pathological conditions. Exact assessment in the ECT setting would required analysis of the raw electroencephalogram (EEG) patterns (75). The BIS value at the time of electrical stimulation has been shown to correlate positively to seizure duration in prospective studies (76–80). BIS value over 55 was highly promising for achieving >30 s of seizure duration (79). A large retrospective study suggests that the seizure induction should be started with a BIS value ≥65 (78). A significant relationship between BIS value and numbers of ECT to remission has been reported in a prospective study, indicating that a higher pre-ECT BIS value results in fewer treatments (77). Although the highest preictal BIS value was 87, no patient reported any memory of ECT procedures (77). The BIS value correlated with higher seizure quality, that is, seizure duration, central inhibition, amplitude, synchronicity and autonomic activation (78). Noteworthy, BIS monitoring does not deliver valid results with ketamine as the anaesthetic-inducing agent (81,82). In a course of successive bilateral ECT treatments in a prospective study, BIS values decreased for each repetition (83). The average baseline BIS value dropped significantly from 92 at baseline to 80 after the sixth bilateral ECT (83). However, this drop in baseline BIS value was not significant nor a tendency in unilateral ECT (78).

ECT and ventilation

Neuromuscular blockade with suxamethonium chloride is required to be sufficiently deep to prevent abdominal muscle contractions in order to avoid aspiration of stomach content into the airways (18), to prevent muscle pain after a myoclonic seizure, to avoid fractures and to secure apnoea during stimulation.

Several studies indicate that hypocapnia prolongs seizure duration (84–87). A retrospective study examining a total of 372 ECT sessions in 37 patients, inducing anaesthesia with ketamine or thiopental, measured the transcutaneous tissue partial pressure of CO_2 and O_2 that is reliably correlated to arterial pCO_2 and pO_2 (64,88). The pO_2/pCO_2-ratio was significantly associated with a better seizure quality sum score and lower amount of administered charge. A retrospective study including a total of 1189 ECT treatments investigated controlled hyperventilation compared with uncontrolled hyperventilation (87). When giving controlled hyperventilation the electrical stimulus was applied when pCO_2 came below 30 mmHg (3.99 kPa) and this group showed significantly longer seizures, lower energy to stimulate, lower maximum heart rate and fewer delirious symptoms than the group with the uncontrolled hyperventilation. It remains possible, however, that the effect of prolonged ventilation merely reflects the effect of time on the depth of anaesthesia, thus ensuring that ECT is given when the anticonvulsive properties of the anaesthetic drug has waned.

Discussion

When the seizure is inadequate, that is, short or unsuccessful the electrical stimulus is increased followed by potentiation of the side effects. When the therapy in itself is without effect the number of treatments is increased. Thus, there is a need to optimise each ECT treatment to lessen the energy and number of treatments.

Anaesthetics

A wide range of drugs are useable in the ECT setting and although the American Psychiatric Association

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recommends methohexital, they acknowledge all the other drugs mentioned in this review as alternatives (89). Thiopental seems to be bested by almost all other drugs when it comes to seizure duration, recovery and haemodynamic stability (23), and only propofol yields shorter seizure durations than thiopental (8). Etomidate yields longer seizures than thiopental and propofol. Etomidate seems promising as an anaesthetic in the ECT setting, with long seizures, few side effects, and good recovery and safety (22–24,71). A 1 : 1 solution of propofol (1.5 mg/kg) plus ketamine (0.8 mg/kg) was well tolerated and seemed promising in three prospective trials (60–62). However, this combination treatment has only been compared with propofol and ketamine as sole agents and needs to be investigated more properly in order to give valid recommendations. If the seizure duration is to be further increased, addition of a low dose of remifentanil should be considered (73).

BIS monitoring seems to be justified in the ECT setting to assess the anaesthetic depth. The BIS value is positively correlated with a better, or at least longer, seizure (78), suggesting that seizure induction should be performed at much shallower anaesthetic depth than usually practised. If BIS monitoring is available it should guide the timing of the seizure induction. However, it is important to bear in mind the necessity of assessing the raw EEG data without which the BIS results are non-informative. A large retrospective study suggested seizure induction to be started at BIS values >65 (78). It is unknown whether the reason that patients have no memory of the ECT procedure even with a high BIS value at the time of induction is because of the seizure by itself or because even a high BIS value grants sufficient anaesthetic depth for obtaining amnesia to ECT procedures. However, repeated bilateral ECT treatments may lower the baseline BIS value thus resulting in a patient being aware with a lower BIS value than expected (83). BIS monitor algorithms are based on healthy subjects and thus may be compromised in pathological conditions.

The pO_2/pCO_2-ratio has been shown to be positively correlated to high-quality seizures in retrospective studies advocating sufficient hyperventilation before seizure induction (64). In the practical ECT setting the time needed for significantly prognostic hypocapnia is far too long for it to be recommended. It could very well be questioned whether the positive effect of increasing the pO_2/pCO_2-ratio should be attributed to the fact that a longer time have passed before inducing the seizure, thus achieving lighter anaesthesia with less central inhibition.

Seizure duration is a simple marker when comparing anaesthetics in ECT and it is often being used synonymously with antidepressant efficacy (73,90). However, a dose–response effect between seizure duration and antidepressant efficacy lacks evidence (91). Many of the studies cited in this review are retrospective studies, thus merely hypothesis generating ones, and they often has 'seizure quality' as outcome measure. The prospective randomised blinded studies on the topic are small and thus large prospective randomised trials on the use of different drugs and the seizure induction timing are necessary. These studies should have antidepressive efficacy, number of ECT treatments and cognitive side effects as outcome measures.

Etomidate or a 1 : 1 ketamine plus propofol combination may be the best method to achieve general anaesthesia in the ECT setting, especially if seizure duration is inadequate. Etomidate being supported by a meta-analysis and propofol : ketamine by randomised controlled trials – which is probably the most valuable scientific work on the subject at the moment (22–24,60,71).

When the course of depth of the anaesthesia is monitorable by BIS value, it may be suggested, however, vaguely supported, that the seizure induction should be started with BIS values ≥65 as long as the patient is not aware (78). The raw EEG data must likewise be assessed. This BIS value-guided timing should be carried out primarily to yield longer seizures.

Large randomised progressive studies comparing the effect of methohexital, thiopental, propofol, ketamine, propofol + ketamine 1 : 1 and etomidate in the ECT treatment of major depressed patients are warranted. These studies should investigate safety and side effects, and most importantly have antidepressant efficacy and cognitive side effects as outcome measures.

Authors Contributions

T.K.S. wrote manuscript. M.B.J. and N.V.O. reviewed and wrote manuscript.

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Conflicts of Interest

None.

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