SOMATO PUBLICATIONS

Current Research in Neurology and Neurosurgery

Research Article

Distinct Effects of Propofol and Methohexital at Titrated Dosages on Hemodynamics, Stimulus Energy, and Seizure Durations during Electroconvulsive Therapy

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Received: 13 February 2018; **Accepted:** 06 April 2018; **Published:** 08 April 2018

Citation of this article: Iqbal, M., Nahi, FT., Hu, Y., Kirchner, HL., Entrup, MH., Zhang, X., et al. (2018) Distinct effects of propofol and methohexital at titrated dosages on hemodynamics, stimulus energy, and seizure durations during electroconvulsive therapy. Curr Res Neurol Neurosurg, 1(1): 001-005.

ABSTRACT

Objectives: Methohexital and protocol are two most common anesthesia induction agents for electroconvulsive therapy (ECT). It is known that methohexital is associated with a lower seizure threshold while propofol produces more favorable hemodynamic responses and recovery. It is unknown, however, if these effects remain unchanged when the drug dosages are adjusted for individual patients. We therefore retrospectively analyzed the effects of propofol and methohexital when their dosages were titrated for desired ECT profile.

Methods: We retrospectively identified the patients who received propofol in May 2014 or methohexital in Oct 2014 for ECT treatments. The following data were collected: dosage of induction agents, heart rates, blood pressures, stimulus energy, electroencephalogram (EEG) seizure duration, and motor seizure duration.

Results: Twenty-two patients (50.2±15.4yo) underwent 83 treatments using propofol (dosage: 1.62±0.38mg/kg, range 1.07-2.67mg/kg) as an anesthesia induction agent. Seventeen patients (50.5±14.1 yo) received methohexital (dosage: 1.01±0.23mg/kg, range 0.56-1.72 mg/kg) for 54 times of ECT. The stimulus energy (% of full charge) needed for seizure induction was significantly higher in the group receiving propofol for induction. The motor seizure duration and EEG seizure duration were significantly shorter when propofol was used for induction. Hemodynamically, the methohexital group had significantly higher HR, SBP and DBP than the propofol group ($p<0.05$).

Conclusions: In conventional clinical practice, dosages of propofol or methohexital adjusted for optimized treatments vary widely between patients. Over such wide range of dosages, methohexital still has a more favorable seizure profile, while propofol has more stable hemodynamics.

Introduction

Every year, general anesthesia has been given repeatedly to about one million patients for electroconvulsive therapy (ECT) worldwide [1]. Several anesthetic protocols, utilizing drugs with distinct pharmacological profiles, appear to be sufficient and safe to mask the electrophysiological activity and the subsequent myoclonic movements [2]. However, it is also suggested that general anesthesia is likely to have therapeutic value by itself, rather than being just a procedure to facilitate another one. Its substantial impact on seizure threshold and energy requirement suggests that general anesthesia may significantly modify ECT therapeutic effectiveness [3,4]. For decades, anesthesia providers, psychiatrists, and other specialists

have been looking for anesthetic agents that are of short duration, promote seizure, and provide stable hemodynamics. Propofol and methohexital are two most commonly used agents and have been extensively studied. The results consistently showed that methohexital was associated with a lower seizure threshold, while propofol produced more favorable hemodynamic responses and recovery [5-7]. Nevertheless, there was no detectable difference on therapeutic effectiveness or cognitive function between these two agents [8,9].

To our knowledge, the dosages of methohexital and propofol in the published studies were all standardized, either using fixed doses [10,11] or titrated to loss of consciousness [5,12,13]. Few clinicians, however, prefer a fixed dosage for anesthesia induction agents [14]. Most providers believe the doses of anesthetic drugs need to be adjusted between patients to accommodate for age and comorbidity, as well as in an individual patient throughout the course of his/her ECT treatments [2]. This is because 1) seizure thresholds vary greatly among patients [15-17], 2) seizure threshold changes over the time of repeated treatments [15,18,19], and 3) sympathetic and parasympathetic responses differ among patients. Therefore, this study undertook to compare outcomes (hemodynamics, stimulus energy, motor and EEG seizure durations) from propofol and methohexital when used in typical clinical fashion where dosage was individualized and adjusted over the course of ECT.

Patients and Methods

This retrospective study was approved by Geisinger Medical Center Institutional Review Board.

Patients

In July 2014, our institutional standard protocol was changed, and the drug of first choice for ECT was changed from propofol to methohexital. To compare the effects of propofol and methohexital, we retrospectively identified the patients who received propofol in May 2014 or methohexital in Oct 2014 for ECT treatment (two near months that had frequent ECT treatments). All cases of ECT in these months were included unless other drugs were used for general anesthesia.

Anesthesia and ECT protocols

Almost half (total 69/137 treatments, 50.4%; propofol group:58/83, 70.0%, and methohexital group: 11/54, 20.3%) of ECT treatments are delivered when patients were hospitalized. No patients received premedication prior to ECT. In post-anesthesia unit, fentanyl or Zofran might be administered if patients complained of pain or nausea. General anesthesia was induced with either propofol or methohexital, and succinylcholine. The initial dosage was estimated based on the American Psychiatry Association (APS) guidelines. The dose for each following treatment could be adjusted based on the seizure duration and patients' responses. For example, if a patient had short seizure time on EEG, the dose of propofol or methohexital would be reduced by 10-20 mg in the next treatment; if patients had a prominent hemodynamic response (systolic blood pressure >160 mmHg or >120% baseline), the dose was adjusted upward for the next treatment. Similarly, dosage of succinylcholine was modified to ensure adequate muscle relaxation and prompt recovery. The initial stimulus energy used was based on patient's age. Face-mask ventilation was initiated after patients lost consciousness at 12-16 breaths/minute. Mild hyperventilation was intended but capnometry did not quantify. ECT stimulation was delivered when fasciculation from succinylcholine was completed (1-2 minutes after administration). All treatments were administered using Thymatron System IV (Somatics, LLC, Lake Bluff, IL, USA). Pulse duration was set at 1.0 ms. EEG seizure duration greater than 25 s was deemed acceptable. Based on seizure duration, energy level might be adjusted by 5-10% each time for the next treatment as needed. No restimulation was given over this period of time.

Data collection

The following data were collected: dosage of induction agent, heart rates (HR), systolic blood pressures (SBP), diastolic blood pressures (DBP), stimulus energy delivered, the electroencephalogram (EEG) seizure duration, and motor seizure duration. Hemodynamic data were collected at baseline (when patient is ready for induction of general anesthesia), T1 (5 min after induction), and T2 (10 min after induction).

Statistical analysis

Data were presented as mean ± standard deviation unless it is stated otherwise. Baseline characteristics were compared between treatment groups using t-test (for continuous variables) and Chi-square test (for categorical variables). To account for the repeated measures, linear mixed models were used to evaluate the effect of treatment over time on the ECT profile and hemodynamics [heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure(DBP)]. Fixed-effects terms included baseline hemodynamic outcomes, time (T1 and T2), treatment groups (methohexital and propofol) and the time by treatment interaction. The random effect associated with the patients was included to capture the correlation of the repeated measures. A p-value less than 0.05 was considered statistically significant.

Results

Patient profile

Twenty-two patients (50.2±15.4yo, body weight 91.6±22.1kg) underwent 83 treatments using propofol (1.62±0.38mg/kg, range 1.07-2.67mg/kg) as an anesthesia induction agent. Seventeen patients (50.5±14.1 yo, body weight 86.5±22.0 kg) received methohexital (1.01±0.23mg/kg, range 0.56-1.72 mg/kg) for 54 times of ECT. Seven (31.8%) in the propofol group and 6 (35.3%) in the methohexital group had only one ECT treatment over that month. Each of the remaining patients had 2-9 treatments. There were only 5 patients who had both propofol in May 2014 and methohexital in October 2014. Comorbidity of coronary artery disease (CAD), hypertension (HTN), diabetes mellitus (DM) and chronic renal disease (CRD) were rare in both groups. Indications for ECT in both groups were mostly major depression disorder (MDD), 68% and 76% respectively. A few patients who needed ECT due to bipolar disorder or schizoaffactive disorder. There were no significant differences in ages, gender, body weight, comorbidity, and indications for ECT between treatment groups (Table 1).

ECT profile

Table 2 presented the results from linear mixed models that compare differences of ECT outcomes between groups. The stimulus energy needed for seizure induction was significantly higher in the group receiving propofol for induction. Both the EEG seizure

duration and the motor seizure duration were significantly shorter in the propofol group (P<0.05).

Hemodynamic profile

Table 3 presented the results from the linear mixed models that compares the differences between groups over time. At T1, patients in propofol group had significantly lower HR (p<0.01). At T2, patients in propofol group had significantly lower HR, SBP and DBP (p<0.01).

Discussion

The findings of this retrospective study are consistent with what has been reported in the past: propofol is associated with more stable hemodynamics, and methohexital with lower treatment energy producing longer seizure duration [5-7]. However, we believe this is the first study to report such findings when the dosing of propofol and methohexital were not standardized to a research protocol. Indeed, the doses of both drugs changed greatly from patient to patient, and some from treatment to treatment for the same patient. In this "real world" clinical setting, we demonstrated distinct pharmacological features between methohexital and propofol. Since clinicians were not constrained to a single induction dosage or shock treatment energy to achieve seizure, one might reasonably anticipate similar ECT responses would be realized between the propofol and methohexital groups. What then caused the difference in the ECT profile and hemodynamics? Although this is not a blinded study, all clinicians were free of bias. At the time of clinical work, there was no intention to compare the drugs. It is thus logical to attribute all the distinct effects on ECT and hemodynamics to their pharmacological features, which remain distinctive over a wide range of doses.

Table 1: Patient profile.

Variable	Propofol N=22	Methohexital N=17	p-value
Male sex	12 (55%)	5 (29%)	p=0.12
Age (years)	50.2±15.4	50.5±14.1	p=0.95
Weights (kg)	91.6±22.1	86.5±22.0	p=0.58
Treatments/case 1 2 3 4 5 6 7 8 9	 7 (32%) 2 (9%) 1(5%) 5 (23%) 2 (9%) 0 3 (14%) 0 2 (9%)	 6 (35%) 5 (29%) 0 1 (6%) 1 (6%) 1 (6%) 2 (12%) 0 1 (6%)	p=0.79
Dosage (mg/kg) [range]	1.62±0.38 [1.07-2.67]	1.01±0.23 [0.56-1.72]	p<0.001
Indication for ECT MDD BD SAD	 15 (68%) 4 (18%) 3 (14%)	 13 (76%) 3 (18%) 1 (6%)	p=0.72
Comorbidity CAD HTN DM CRD	 3 (14%) 8 (36%) 4 (18%) 2 (9%)	 3 (18%) 7 (41%) 2 (12%) 1 (6%)	p=0.91

MDD: Major Depressive Disorder; BD: Bipolar Disorder; SAD: Schizoaffactive Disorder; CAD: coronary Artery Disease; MD: Diabetes Mellitus; CRD: Chronic Renal Disease.

Table 2: ECT profile.

Groups	Energy (%)*	Seizure (S)	EEG (S)
Propofol (n=22)	59.3±24.1	15.0 ±10.1	36.8 ±11.7
Methohexital (n=17)	43.5±20.8	21.5±15.9	57.1±37.0
p-value	p<0.05	p<0.05	p<0.001

*: Full charge (100%) is 504 mC.

Table 3: Hemodynamic profile.

Parameters	Groups	Baseline	T1	T2
HR (BPM)	Propofol	77.1±13.5	77.1±13.5	78.8±14.7
	Methohexital	79.5±17.7	91.0±22.7	91.4±21.9
	p-value	>0.05	<0.001	<0.001
SBP (mmHg)	Propofol	132.1±14.1	135.1±17.7	130.8±20.8
	Methohexital	127.1±28.5	134.4±26.8	144.5±24.0
	p-value	>0.05	>0.05	<0.001
DBP (mmHg)	Propofol	76.3±9.5	79.6±14.2	76.6±12.9
	Methohexital	77.9±11.0	81.5±15.9	87.7±20.9
	p-value	>0.05	>0.05	<0.01

HR: Heart Rates; SBP: Systolic Blood Pressure; and DBP: Diastolic Blood Pressure.

In theory, these findings might support the use of methohexital over propofol unless there is a concern over heart rate or blood pressure changes. Longer seizure duration with lower treatment energy might be a perfect combination for therapeutic value and avoidance of cognitive impairment. Unfortunately, many randomized clinical studies, comparing methohexital to propofol, had found a dissociation between a favorable ECT profile (low treatment energy and longer seizure time) and better outcomes (depression improvement and restoration of cognitive functions) [6-8]. This is also to support the suggestion that seizure duration has limited relevance to the efficacy of ECT [20,21]. Neither could we find any study that confirms the cardiovascular advantage of propofol over methohexital, measured as frequency of adverse cardiovascular event following ECT. Hemodynamic changes following electrical stimulation are profound, and severe bradycardia and/or tachycardia, hypotension and/or hypertension are very common. However, they are all transient, and serious cardiovascular events, such as myocardial infarction, heart failure, and asystole were believed to be rare [22,23]. Therefore, any hemodynamic "benefit" attributed to propofol for ECT remains speculative.

Regardless which induction agent one chooses, our results indicated that careful dosing/titration might be as critical as selecting agents. As pointed out by Ding and White [2], "the optimal dosages of anesthetic, muscle relaxants, and sympatholytic drugs require careful titration to the needs of individual patient, and further adjustment should be made during the course of a serious of ECT treatment on the basis of the patient's earlier responses." We found a wide range of doses for each drug. The doses for methohexital recommended by the American Psychiatric Association is 0.5-1.0 mg/kg, and propofol 0.75- 1.5 mg/kg [24]. The dosages we used were 0.56-1.90 mg/kg for methohexital and 1.08-2.67mg/kg for propofol. We believe this

reflects the differences in inter-patient seizure thresholds [15-18] and intra-patient variation of seizure thresholds over the course of treatments [15,18]. The difference in seizure threshold could be as high as 50 folds among psychiatric patients [16,17]. It was found that changes of seizure threshold over the treatment courses are associated with previous history of ECT treatments [15-18]. The seizure threshold of patients without previous ECT may increase over the course of treatment while patients with previous ECT had a trend of decreasing seizure threshold [15]. Had we used fixed doses for either drugs, ECT profile and hemodynamics might be less desirable. It remains unknown if careful dose adjustment of methohexital and propofol could further improve treatment outcomes.

There are a few limitations of this retrospective study. First, since we included every patient within the research periods who was in different cycle of treatments. Some had only one treatment within that month, while others had up to 9 treatments. Ideally, a homogenous group of patients who are in similar treatment cycles, may be preferred to study inter- and intra- patient variations. Secondly, our patients appeared to be young (~50s yo) and rarely had comorbidity. Therefore, the importance of hemodynamic stability during ECT treatment may not be as critical as it would be to a frailer patient cohort. Thirdly, we used and studied only a single induction agent for each ECT. It is possible that an optimal anesthesia might be a combination of different agents. For example, it has been shown that ketamine itself has profound anti-depression effects [25]. However, ketamine alone for ECT may suffer from its increased secretion, tachycardia, post anesthesia nausea and vomiting, and delayed emergence. A small dose of ketamine might provide considerable benefit with little side effect for the ECT treatment [26]. So far this remains controversial. A recent report by Fernie et al. [27] showed that ketamine did not improve efficacy of ECT. Currently, studies do not support using ketamine as an adjunctive agent in routine ECT treatments [28,29].

In summary, our data indicate that for desired seizure duration and timely recovery, dosages of propofol or methohexital varied widely from patient to patient. When dosages were titrated based on prior ECT response, methohexital provided a more favorable ECT profile (lower energy requirement and longer seizure duration), but less smooth hemodynamic response during treatment. In contrast, patients who received propofol showed less hemodynamic response variability, but needed higher treatment energy and experienced shorter seizure durations. Our results suggest that propofol and methohexital have distinct hemodynamic and ECT responses over a wide range of doses.

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