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Post-electroconvulsive therapy recovery and reorientation time with methohexital and ketamine: a randomized, longitudinal cross-over design trial

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Abstract

Objectives—Methohexital, a barbiturate anesthetic commonly used for electroconvulsive therapy (ECT), possesses dose-dependent anticonvulsant properties, and its use can interfere with effective seizure therapy in patients with high seizure thresholds. Ketamine, a NMDA-antagonist with epileptogenic properties not broadly used for ECT inductions, is a commonly used induction agent for general anesthesia. Recent studies suggest that the use of ketamine is effective in allowing successful ECT treatment in patients with high seizure thresholds without an increase in side-effects. In this preliminary study, we directly compared the recovery and re-orientation times of subjects receiving ketamine and methohexital for ECTs.

Methods—Twenty patients were randomized in a cross-over design to receive methohexital and ketamine for ECT inductions in alternating fashion for six trials. Primary outcome measures were recovery time (voluntary movement, respiratory effort, blood pressure, consciousness, and O₂ saturation) and re-orientation time. Secondary outcome measures were individual recovery variables, side-effect occurrence, and seizure duration.

Results: Overall recovery time was not significantly different between the two treatment arms ($F(1,17) = 0.72$, $P = 0.41$). Re-orientation time was faster in the methohexital arm ($F(1,17) = 9.23$, $P = 0.007$).

Conclusion—Ketamine inductions resulted in higher number of side-effects, higher subject dropout rates, and a longer reorientation time with respect to methohexital inductions. No

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significant difference in post-anesthesia recovery time was found between the ketamine and methohexital arms. Intolerability to ketamine affected a significant proportion of subjects, and suggests that ketamine should remain as an alternative or adjunctive agent for patients with high seizure thresholds.

Keywords

Electroconvulsive therapy; ketamine; methohexital; recovery; reorientation

Introduction

When preparing a patient for electroconvulsive therapy (ECT), the anesthesiologist's choice of the type and dose of induction agents must balance what is needed to render the patient sufficiently anesthetized without interfering with seizure induction or duration. Many safety and efficacy studies have compared the effects of these induction agents on seizure duration, intensity, disorientation time, and treatment outcome¹⁻¹³. In the last decade, the use of ketamine for ECT treatments has shown potential benefits due to its ability to lower the seizure threshold and decrease disorientation and retrograde amnesia^{5, 9-11, 14-17}. The mechanism of its effect on attenuating impairment is unknown, but it has been suggested that its action as an NMDA antagonist may have a protective role in reducing the excitatory neuronal damage seen after seizures⁵. Ketamine has also been suggested to have inherent antidepressant effects, which can improve the efficacy of the treatment^{14, 17, 18}. However, the routine use of ketamine may be limited due to concerns about side effects including psychosis, hypertension, tachycardia, increased intracranial pressure, and prolonged disorientation^{2, 19}, but the safety and efficacy of ketamine was supported in a retrospective study in patients that could not achieve adequate seizure duration with a methohexital induction despite reaching maximal stimulus intensity¹¹. However, a more recent study suggests that the anti-depressant benefits of using ketamine for ECT may not be as strong as previously thought, and the side-effects of ketamine may outweigh the benefits when used as a sole induction agent²⁰.

In this cross-over, prospective study, our primary aims were to systematically assess the recovery time and time to reorientation of ECT patients induced with ketamine or methohexital, since these are two frequent areas that can delay a patient's discharge from the post-anesthesia recovery unit. Based on a prior retrospective study¹¹ and purported neuroprotective effects of ketamine⁵, we hypothesized that ketamine would be associated with (1) a faster recovery time and (2) a faster time to reorientation relative to methohexital.

Methods

The Human Research Review Committee at the University of New Mexico Health Sciences Center (Albuquerque, NM) approved this study, and the protocol was registered prospectively with ClinicalTrials.gov (NCT01567852). All subjects provided written informed consent prior to participation in this single-blinded, crossover, randomized clinical trial.

All ECTs were performed at University of New Mexico Hospital Post Anesthesia Care Unit. Inclusion criteria were diagnosis of a depressed episode in either bipolar or unipolar depression, American Society of Anesthesiology (ASA) physical status classification status of III, age > 18, and possessing decisional capacity for research consent. Exclusion criteria included primary psychotic disorders, an ASA status > 3, a known allergy to ketamine or methohexital, uncontrolled severe hypertension, a current or previous history of intracranial hypertension, bleeds or aneurysm, or current pregnancy.

The order for which drug was given first was randomized in blocks of six. The induction agents used alternated for each subsequent ECT. Subject participation was discontinued if the subject expressed refusal to receive either one of the induction agents. Half of the patients were randomized to receive ketamine for the first ECT, the other half methohexital. The anesthesiologist and psychiatrist were not blinded to the induction agent used. An envelope containing the schedule of induction agent to be used for each treatment was given to the anesthesiologist at the beginning of each trial. Research assistants who gathered recovery and reorientation data were blinded to the induction agent, and all treatments occurred behind an opaque drape.

The anesthesiologist employed a starting dose of 1 mg/kg of either methohexital or ketamine, according to randomization, with titration of dosage done as necessary for complete induction of anesthesia. Doses were not to exceed 1.5 mg/kg. If the patient exhibited hypertension or tachycardia of greater than 20% of their baseline, the anesthesiologist had the discretion to treat with labetalol, esmolol, hydralazine, or nitroglycerin until the values returned to baseline. The anesthesiologist was also free to treat pain and nausea associated with the procedure, and these symptoms and treatments were recorded.

ECT was performed using a Thymotron System IV. All patients received right unilateral stimulus with an ultra-brief pulse width (0.25 ms). The first ECT session determined the seizure threshold with subsequent sessions delivering a percent energy six times the seizure threshold. Short seizure durations (< 25 seconds) or poor post-ictal suppression resulted in an incremental increase in percent energy. The six ECT sessions used in this investigation started after stimulus titration. The percent energy was not re-titrated for the specific induction agents. All patients were concurrently treated with antidepressant medications during this investigation. Dosage titration did occur during this trial but patients were not started on new agents during this investigation.

The primary outcomes were 1) the overall recovery time and 2) the time to reorientation. Start time for these indices was the end of EEG seizure activity. Overall recovery was assessed with a scoring mechanism that measured movement, respiration, circulation (blood pressure), consciousness, and oxygen saturation (**Table 1**) since these are commonly used criteria for evaluating discharge readiness from the Post Anesthesia Care Unit ²¹. Reorientation was assessed with 5 questions (name, age, location, year, day of week). For both outcomes, a score was obtained pre-procedure, at 1 minute post-procedure, and every 5 minutes thereafter until the participant achieved the pre-procedure score. The procedure end time was set to be the time when EEG seizure ends, as determined by the treating

psychiatrist. The time at which scores returned to baseline was recorded. Data collection was truncated at 60 minutes. Secondary outcomes included the individual criteria from the recovery score (movement, respiration, circulation, consciousness, O₂ saturation) and seizure duration. We also assessed differences in the number of adverse events (pain, nausea, neurologic or psychotropic impairment).

A linear mixed model with random effects for patients and fixed effects for drugs (ketamine or methohexital) using first order auto-regressive covariance structure fit with SAS version 9.3 assessed differences in primary and secondary outcomes. The linear mixed models also assessed order effects by drug. The Exact McNemar test assessed differences in the occurrence of side effects between ketamine and methohexital. Required sample size was assessed using significance level 0.05 and power of 0.80 for a two-sided test in the cross over design. A clinically meaningful difference in recovery times was assumed to be 5 minutes. Reported variability in the literature has a wide range so a value at the upper range (21.5 minutes) was assumed. Within-subject correlation was assumed to be approximately 0.7. With these assumptions for this design, a total of 20 subjects was expected to yield a power of at least 0.8.

Results

A total of 20 patients (average age 53 years $\pm$ 17, 8 males, average ASA rating 2.25 $\pm$ 0.44) were enrolled in the study. Demographic data for each subject are presented in **Table 2**. Ten patients withdrew because of side effects from the induction agent that was later identified as ketamine. Only one patient withdrew secondary to side effects from methohexital. Two more patients finished the ECT series prior to completing the study protocol. Seven subjects completed the entire protocol. The patient flow is summarized in **Figure 1**.

Primary Outcomes

Our primary outcomes included the time to achieving baseline scores on all recovery criteria and time to re-orientation. The time it took to for patients to meet all baseline recovery scores was not significantly different between ketamine and methohexital ($F(1,17) = 0.72$, $P = 0.41$). In contrast, reorientation time was faster for methohexital relative to ketamine ($F(1,17) = 9.23$, $P = 0.007$). Order effects were not significantly different between groups on both primary outcomes ($P > 0.05$). Because of the high number of dropouts, the analysis was repeated with subjects who did not withdraw from the study ($n = 9$). Among study completers, the methohexital trials were still associated with a faster reorientation time ($F(1,8) = 6.49$, $P = 0.03$). In a post-hoc analysis, we also assessed differences in dropouts related to ketamine versus methohexital with the exact binomial test. The subjects who dropped out secondary to ketamine ($n = 10$) were greater than the subjects who dropped out secondary to methohexital ($n=1$) ($P = 0.01$). Our primary and secondary outcomes are presented graphically in **Figure 2** and summarized in **Table 3**.

Secondary Outcomes

Our secondary outcomes included the time to return to baseline scores for each individual criteria of our recovery score (movement, respiration, circulation, consciousness, and oxygen saturation), seizure duration, and occurrence of side effects. Methohexital trials had shorter recovery times for movement ($F(1,17) = 5.89, P = 0.03$) and consciousness ($F(1,17) = 20.03, P < 0.001$). Respiration, circulation, and oxygen saturation recovery times were not significantly different between methohexital and ketamine ($P > 0.05$). We also assessed order effects. Only the circulation recovery times had an order effect that was associated with type of induction agent ($F(1,46) = 7.72, P = 0.008$). The circulation recovery time, defined as the return to within 20% of baseline blood pressure, took longer in the later trials with ketamine. We did not find a significant difference in specific side effects between the two groups ($P > 0.05$). The ketamine group had a larger number of summed side effects relative to methohexital ($P = 0.03$). These results are presented in **Table 4**. Seizure duration was shorter for methohexital relative to ketamine ($F(1,17) = 8.9, P = 0.008$).

Discussion

In this pilot study, we compared ECT recovery and re-orientation times between ketamine and methohexital inductions. The most notable result was the high rate of intolerability related to the side-effects of ketamine, which led to a disproportionately high subject withdrawal rate in the ketamine arm as compared to the methohexital arm. With respect to our primary aims, we did not find a significant difference in the time it takes to achieve a baseline score on our recovery criteria, and, contrary to our hypothesis, the methohexital trials were associated with a faster reorientation time relative to ketamine by 5 minutes. Our secondary outcomes also failed to support our hypothesis. The ketamine trials were associated with more dropouts and an increased number of side effects.

The major finding of this investigation was the high dropout rate related to ketamine. Many of the patients withdrew after the first or second time they received ketamine, citing a strong preference for the alternate agent (methohexital) due to the nausea, dysphoria, and dizziness that lasted from half a day to three days. These results support the recent study by Rasmussen et al.²⁰ that suggests the side-effect profile of ketamine leads to a higher number of subject withdrawal, while recovery time is not decreased when compared to methohexital. While we did not determine significant differences in specific side-effects between the two groups, the total number of side-effects was increased for the ketamine arm. Our study was not powered for side-effect analysis, and we predict that a larger study specifically powered for such would demonstrate a more significant difference with specific side-effects.

While we did not observe a significant difference in the time it takes to achieve a baseline score for all recovery criteria, we did detect a shorter time for recovery of voluntary movement and return of consciousness with the methohexital arm in our secondary outcomes. There are multiple variations on scores used to evaluate whether patients are ready for discharge from the PACU, and in this study, we elected to use a simple and easy to measure criteria that would eliminate, as much as possible, the need for the observer to make subjective judgments regarding what score to assign. This scoring system is frequently

modified based on individual hospital protocols, and it is very possible that depending on the scoring criteria used, the results for “recovery” may yield different results.

In contrast to the previously cited study that demonstrated decreased re-orientation times with ketamine inductions¹¹, our results demonstrated a prolonged re-orientation time. A post hoc analysis of only those subjects that completed the trials still demonstrated a significant prolongation of reorientation time with ketamine as compared to methohexital. The cited study was accomplished via a retrospective analysis of only patients that were unable to be treated successfully with methohexital¹¹. The difference in study design may account for the difference in our finding, as the difference in seizure thresholds of our patient populations may affect the degree of post-ictal disorientation as well as alter the degree to which ketamine may contribute to the disorientation. This longer reorientation time may be due to the compounding effects of the post-ictal state and the dissociative anesthetic nature of ketamine. Methohexital is an oxybarbiturate that produces anesthesia through the enhancement of GABA activity in the central nervous system (CNS). Ketamine is an arylcyclohexylamine that produces CNS depression through inhibition of thalamocortical pathways, at the same time stimulating the limbic system. These different mechanisms of action, along with the slightly longer context sensitive half-life of ketamine (20 - 30 min)¹⁹ compared to methohexital (4 - 22 min)^{22, 23}, may account for the longer reorientation time.

This investigation has some limitations. First, the high withdraw rate heavily limited the power of this study, and while we observed some trends, we could not achieve significance in several areas where we felt a larger study group would have aided in that respect. These areas include hemodynamic recovery and side-effect profiles. Second, we did not re-titrate the seizure threshold when we changed induction agents. Our subjects were typically consented after the third treatment, and we continued to use the same percent energy for the remaining trials, only making adjustments if the seizure morphology was suboptimal. Subsequently, the ketamine trials may have been associated with a higher stimulus delivery relative to the threshold that would have been established with a ketamine specific titration. The prospect of devoting two sessions from an ECT series to determine induction agent specific seizure thresholds would be an elegant intervention but must be balanced with the possibility of slowing recovery from multiple sub-optimal treatments (i.e., treatments performed at less than six times seizure threshold). Third, different anesthesia providers employed different thresholds and doses when administering vasoactive agents to control the cardiovascular side effects of the post-treatment phase, which may also have confounded our recovery data, although we did not find a significant difference in vasoactive agent doses between the two arms. Fourth, we may have affected our side-effect profiles with routine administration of anti-emetics and non-steroidal analgesic agents, thus contributing to the null hypothesis for this outcome. Furthermore, concurrent anti-depressant pharmacotherapy was not controlled for, and while the cross-over design minimized the confounding effects of patient co-morbidities and routine medications, rapid changes in medical condition might still have contributed confounding effects. Finally, the results of this study cannot be generalized to bi-temporal treatments.

Conclusions

A disproportionate intolerability to ketamine as compared to methohexital was evident in our trial. Ketamine was associated with a higher subject drop-out rate, increased side effects, and increased re-orientation time relative to methohexital, with no observed reduction in post-anesthesia recovery time. Given the observations from this preliminary trial, we question whether the routine use of ketamine for the induction of general anesthesia in ECT patients would be tolerated enough to allow broader clinical use. Within the psychiatry community, there has been a resurgence of interest in the use of ketamine to treat cases of depression^{10, 14, 17, 24}. These studies have examined the use of both boluses or infusions of ketamine. The high ketamine-associated dropout rates in our trial suggest that tolerability may be an issue that many patients and practitioners may struggle with. This intolerance may be dampened through use of lower-dose infusions, since infusion pharmacokinetics of a given drug differs from those of boluses of the same drug²⁵. However, in the context of an induction agent for ECTs, it appears that rather than as a first line agent, the role of ketamine should remain as an alternative or adjunctive agent for patients that possess high seizure thresholds for which other agents have failed to achieve adequate anesthesia and seizure activity.

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Figure 1.

Patient flow: 20 subjects were enrolled, with 11 withdrawals prior to completion of study. 7 completed all 6 trials, while 2 completed their ECT course before 6 trials were done. 10 subjects withdrew because of the side-effects of ketamine, while 1 withdrew due to methohexital.

Figure 2.

Time required for primary outcomes to return to baseline. Left: Time required for all recovery criteria to return to baseline. Right: Time required for reorientation to baseline score. Individual trial times are depicted. Lines shown depict average times for each trial. D represents subject withdrawal after that trial.

Table 1**Scoring Criteria Used to Measure Recovery**

Criteria Used to Measure Recovery	Score
Movement: Ability to move voluntarily or on command	
Four extremities	2
Two extremities	1
Zero extremities	0
Respiration	
Able to deep breathe and cough freely	2
Dyspnea, shallow or limited breathing	1
Apneic	0
Circulation	
Blood Pressure +/- 20 mmHg of baseline	2
Blood Pressure +/- 21-50 mmHg of baseline	1
Blood Pressure +/- 51 mmHg of baseline	0
Consciousness	
Fully awake	2
Arousable on calling	1
Not responding	0
O ₂ Saturation	
Able to maintain saturation > 90% on Room Air	2
Needs supplemental O ₂ to maintain saturation > 90%	1
Saturation < 90% even with supplemental O ₂	0

Table 2

Demographics and clinical variables

ID	Age	Gender	Ethnicity	ASA	Psych Diagnosis	Completed study?
1	54	F	W	2	MDD	Yes
2	48	M	W	2	MDD	Yes
3	59	M	W	2	Bipolar	No ^{**}
4	57	F	H	3	MDD	No ^{**}
5	71	F	W	2	MDD	Yes
6	46	M	W	2	Bipolar	Yes
7	61	M	W	3	MDD	No [*]
8	77	F	W	2	MDD	No ^{**}
9	83	F	H	3	MDD	Yes
10	28	F	W	2	MDD	Yes
11	49	F	H	2	MDD	No ^{**}
12	59	F	H	2	MDD	No ^{**}
13	59	F	H	2	MDD	No ^{**}
14	31	M	O	2	MDD	Yes
15	69	M	W	2	MDD	Yes
16	23	M	W	2	Bipolar	No ^{**}
17	34	F	W	2	Bipolar	Yes
18	25	F	W	3	Bipolar	No ^{**}
19	57	M	W	3	MDD	No ^{**}
20	63	F	W	2	MDD	No ^{**}

Yes = completed study;

^{*}No = discontinued study secondary to methohexital trial;^{**}No = discontinued study secondary to ketamine trial; M = male, F = female; W = Non-Hispanic Caucasian, H = Hispanic Caucasian, O = Other; MDD = Major Depressive Disorder

Table 3

Primary and secondary outcome measures

<i>Primary</i>	Methohexital	Ketamine	f (P)
Recovery time (min +/- se)	27.2 (+/-1.7)	28.6 (+/- 2.0)	0.72 (0.41)
Reorientation time (min +/- se)	19.5 (+/-1.6)	24.5 (+/-1.6)	9.23 (0.007)
<i>Secondary</i>			
Movement (min +/- se)	12.6 (+/-1.0)	15.2 (+/-1.0)	5.89 (0.03)
Respiration (min +/- se)	12.5 (+/- 1.1)	13.7 (+/- 1.0)	1.30 (0.27)
Circulation (min +/- se)	22.9 (+/- 4.4)	15.9 (+/-3.5)	2.51 (0.13)
Consciousness (min +/- se)	18.0 (+/- 1.6)	25.3 (+/- 1.7)	20.3 (< 0.001)
O2 saturation (min +/- se)	22.8 (+/- 2.0)	23.2 (+/- 1.9)	0.06 (0.81)
Seizure duration (sec +/- se)	43.3 (+/- 4.6)	55.9 (+/- 3.4)	8.9 (0.008)

Table 4

Number of Subjects with Side effects

Side Effect	Only with Methohexital	Only with Ketamine	With Both	P-value
Nausea	0	4	1	0.125
Anxiety	0	0	1	1
Dysphoria	0	4	0	0.125
Headache	1	2	0	1
Recall	1	0	0	1
Dizziness	1	2	1	1
Agitation	0	1	0	1
Lethargy	2	2	0	1
Hallucination	0	1	0	1
Total	5	16	3	0.03