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A randomized comparison of ketamine versus methohexital anesthesia in electroconvulsive therapy

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ABSTRACT

To assess the clinical utility of ketamine as an anesthetic agent for electroconvulsive therapy (ECT), based upon recent findings that ketamine may have antidepressant properties. Depressed ECT patients were randomly assigned to receive anesthesia with either ketamine or methohexital. Outcome measures included assessments of depressive severity, cognition, post-anesthesia side effects, and hemodynamics. Twenty one patients were treated with ketamine and 17 with methohexital. There were no significant differences in depression or cognitive outcomes between the two drugs. Additionally, there were no measures of post-anesthesia tolerability or hemodynamics which favored ketamine. Ketamine anesthesia does not accelerate the antidepressant effect of ECT or diminish the cognitive side effects, at least as measured in this study. Furthermore, there is no apparent benefit of ketamine for speed or quality of post-ECT recovery, and it is associated with higher systolic blood pressures after the treatments. Ketamine is associated with longer motor seizure duration than methohexital.

1. Introduction

The n-methyl-d-aspartate (NMDA) receptor blocking agent ketamine has been studied as an antidepressant agent, with several placebo-controlled trials indicating that even a single small dose, typically 0.5 mg/kg, can effect rapid benefit (Berman et al., 2000; Zarate et al., 2006; Diazgranados et al., 2010). Based on these findings, there has been interest in the use of ketamine to enhance the antidepressant efficacy of ECT. There are three comparative trials using ketamine to augment other anesthetics. In one (Loo et al., 2012), ketamine augmentation of thiopental anesthesia, compared to placebo augmentation of thiopental, appeared to be associated with enhanced reductions in depression ratings after the first week of treatment but not at 2 weeks or at the end of treatment. Abdallah et al. (2012) also compared ketamine augmention of thiopental to thiopental alone and found that ketamine was not associated with any acceleration of the antidepressant effect of ECT. Jarventausta et al. (2013) found that ketamine augmentation of propofol anesthesia did not enhance or accelerate the antidepressant efficacy of ECT with propofol alone.

In two trials in which ketamine was used as the sole anesthetic, Wang et al. (2012) only treated patients with ECT on one occasion, which differs markedly from routine clinical practice, and Okamoto et al. (2010) did not assign patients to anesthetic group randomly, which detracts from the scientific quality of the data. However, both of those trials did find evidence, like Loo et al. (2012), that ketamine was associated with an early enhancement of the antidepressant effect of ECT that was not sustained by the end of the treatment course. There is a need for further research to elaborate the role of ketamine as the sole anesthetic compared to another anesthetic during a course of ECT to assess depression outcomes. Additionally, there has been some suggestion from basic science literature that ketamine may protect against the cognitive side effects of ECT (Rasmussen et al., 1996; MacPherson and Loo, 2010). Herein, we report the results of a randomized controlled trial comparing anesthesia during ECT with ketamine versus methohexital utilizing outcome assessments of depression and cognition. We also assessed other variables to test the tolerability and safety of ketamine anesthesia for ECT, including post-treatment side effects and hemodynamics.

2. Methods

2.1. Study scheme

The study was approved by the Institutional Review Board of the Mayo Clinic. All participants signed informed consent. Patients were randomly assigned to

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receive methohexital or ketamine as anesthetic during the first six treatments of their course of ECT. The personnel in the ECT suite were not blind to anesthetic agent. However, the patient was not told which drug they were receiving. The post-anesthesia recovery nurses who performed the recovery room outcome measures were also not told which anesthetic drug was used and did not have access to that information. Finally, the primary referring psychiatrist as well as all other personnel on the inpatient units were blind to anesthetic drug assignment.

Inclusion criteria consisted of presence of a non-psychotic major depressive episode, whether unipolar or bipolar. Only patients providing their own consent for ECT were approached for the study. Excluded were patients diagnosed with any psychotic or major neurological disorder.

The randomization scheme was kept by the ECT nurse who notified the anesthesiologist attending the first treatment session which study drug that patient was to receive. Starting doses of 1.0 mg/kg were targeted for both methohexital and ketamine and were modified accordingly on a case by case basis. All patients were pre-medicated at each ECT session with glycopyrrolate as an anti-sialogogue and were paralyzed after anesthesia with succinylcholine. Continuous postive pressure ventilation with 100% oxygen was undertaken at the time of apnea until resumption of spontaneous respiration post-ictally. Monitoring consisted of continuous ECG and pulse oximetry along with regular blood pressure measurements. Electrode placement was determined by the patients' primary referring psychiatrists. Electrical dose titration was used to determine seizure thresholds at the first session. Subsequent dosing consisted of 1.5 times threshold for bitemporal and 6 times threshold for unilateral placement. Pulse width was 1.0 ms for bitemporal and 0.25 ms (i.e., "ultrabrief") for unilateral. The ECT apparatus was a Thymatron DGX (Lake Bluff, IL, USA).

2.2. Outcome measures

There were four domains of outcome assessment: depression, cognition, recovery side effects, and hemodynamics. To assess depression severity, we utilized two self-report depression scales: the PHQ-9 (Kroenke et al., 2001), which is a nine-item questionnaire, and the Hospital Anxiety and Depression Scale (HADS; Snaith and Zigmond, 1994), which is a 14 item questionnaire. Cognition was assessed with the Mini Mental State Exam (MMSE; Folstein et al., 1975). These three measures were administered at baseline and after treatments two, four, and six on the mornings of the next scheduled treatments. For patients whose treatment series was completed prior to a scheduled next administration of these rating scales, every effort was made to administer them 2 days after the last treatment. Number of treatments in the course was determined by the primary psychiatrists and not by scores on the HADS or PHQ-9.

Post-treatment side effects were assessed at the time of discharge from recovery with five self-report items: nausea – headache – myalgia – visual disturbance – confusion. These were rated by the patients on a four point scale (0=absent, 1=mild, 2=moderate, 3=severe). Also, degree of recovery room agitation was rated by the (blinded-to-anesthetic drug) recovery nurse on a similar four point scale. Time spent in the ECT suite as well as in the recovery area were abstracted from the anesthesia records. Post-treatment orientation was assessed with a 10 item questionnaire administered 20 min after the end of the seizure. The 10 items were age, birth year, season of year, year, month, day of month, day of week, name of hospital, city, and state. The score was the number of questions answered correctly. Blood pressure and pulse were recorded at time of discharge from the ECT suite as well as from the recovery area.

2.3. Statistical analysis

To derive sample size, we used the Okamoto et al. (2010) data measuring depression response to ECT, yielding an effective sample-size of $N=17$ per group to provide statistical power of 80% to detect a difference between groups of 1.2 standard deviations using a two-sided, alpha=0.0125 (Bonferroni corrected) test.

Outcomes and measures across all visits are summarized using means and standard deviations by drug. Statistical comparisons of repeated outcomes and measures by drug were made using longitudinal mixed models. Comparisons of the model-based estimates were configured to test the differences by drug over the course of all treatments. Longitudinal models incorporated all observations for all study patients, regardless of number of treatments. Statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

3. Results

3.1. Enrollment and demographics

There were 38 patients (24 female, 14 male) who signed consent to enroll in the study and who received at least one ECT treatment with the assigned study drug. Seventeen of these were randomized to methohexital (8 female, 9 male) and 21 to ketamine (16 female, 5 male). Mean age ($\pm$ standard deviation) in years of all patients who received at least one study treatment was 48.6 ($\pm$ 7.2) for methohexital and 47.0 ($\pm$ 13.2) for ketamine.

Three patients dropped out of the study, one due to perceived worsened tinnitus with ketamine, one due to fear of side effects with ketamine, and one due to dropping out of ECT. Additionally, in three patients a non-study-assigned anesthetic was used during at least one of the treatments due to a miscommunication with the anesthesiologist, so only data pertaining to individual treatments in which the assigned study anesthetic was used were analyzed for those patients. Also, if such a patient had at least one depression rating scale and MMSE after the first two treatment sessions in which the assigned study anesthetic drug was used, then those outcome data were analyzed. In the methohexital group, 9 patients received bitemporal electrode placement, 7 unilateral, and 1 mixed. In the ketamine group, 10 received bitemporal, 10 unilateral, and 1 mixed.

3.2. Outcome measures

Results of the statistical analyses are presented in Table 1. There was no significant difference in scores on either depression rating scale or in MMSE or post-treatment orientation scores. There was no signal indicating a therapeutic advantage with ketamine at any of the time points.

Post-ictal subjectively reported confusion was greater with ketamine than with methohexital. All other recovery side effects were not significantly different between the two anesthetics. However, there were some notable trends that just missed significance at the $p<0.05$ level: recovery orientation scores were slightly lower, and nausea and visual disturbance scores slightly higher, with ketamine. There was no significant difference in time in the ECT suite or time in recovery between ketamine and methohexital. Systolic blood pressures were higher at both time points for ketamine. There was no significant difference in pulse rates or diastolic pressure.

Other measures were assessed. Motor seizure duration was significantly longer with ketamine. We also recorded total number of concomitant psychotropic medications patients received during their courses of ECT as well as usage of intra-procedural medications such as labetalol, esmolol, ondansetron, and ketorolac and found no difference between the two anesthetics. No post-ictal sedatives, such as midazolam or diazepam, were used. There was also no difference in electrical dosing used to induce the seizures. Finally, the doses of ketamine and methohexital were virtually identical at about 1.04–1.05 mg/kg.

4. Discussion

We found no evidence that ketamine hastens the antidepressant activity of ECT, similar to two other studies (Jarventausta et al., 2013; Abdallah et al., 2012). This is in contrast to three studies, one utilizing ketamine to augment thiopental anesthesia (Loo et al., 2012) and two utilizing ketamine alone for anesthesia (Okamoto et al., 2010; Wang et al., 2012), which show initial greater reductions in depression severity with ketamine (i.e., during the first few days to a week or so), but no ultimate benefit over time. A retrospective chart review study (Kranaster et al., 2011) purportedly found a benefit of using s-ketamine for ECT anesthesia in terms of lesser treatments given than with the comparator anesthetic, but the study was not randomized and involved very small sample sizes. It is possible, taking into account the extant literature, that ketamine use at ECT may hasten antidepressant activity early on, but the effect size seems small, the benefit is temporary, and the clinician must balance this

Table 1
Outcome data.[a]

Outcome	Ketamine			Methohexital			
	N[c]	Mean	S.D.	N[c]	Mean	S.D.	p
Total meds[b]	21	2.76	1.34	17	3.35	1.37	0.271
Dose mg/kg	105	1.05	0.22	88	1.04	0.22	0.482
Electrical dose (mCoul)	105	148.56	84.16	89	183.76	117.11	0.265
Motor duration (s)	97	38.45	15.69	85	28.06	22.66	0.017
EEG duration (s)	102	57.78	23.64	87	48.95	25.24	0.185
ECT time (min)[d]	105	11.07	3.10	89	9.93	2.37	0.071
Recovery time (min)	105	13.19	4.49	89	12.38	3.60	0.225
PHQ-9	65	15.98	7.54	63	17.57	6.96	0.258
HADS	54	22.08	8.11	55	24.45	7.70	0.171
Orientation	87	5.97	3.64	83	7.54	3.04	0.085
Nausea	85	0.12	0.39	81	0.15	0.42	0.091
Headache	85	0.29	0.61	81	0.35	0.67	0.763
Muscle ache	83	0.07	0.30	81	0.15	0.48	0.356
Confusion	84	0.70	0.95	81	0.30	0.53	0.003
Visual disturbance	83	0.08	0.28	81	0.01	0.11	0.093
Postictal agitation	84	0.07	0.26	82	0.09	0.36	0.860
Systolic pressure 1[e]	99	155.70	27.13	85	140.25	25.93	0.018
Diastolic pressure 1	99	90.23	19.05	85	88.06	18.55	0.630
Pulse 1	99	95.77	23.55	85	95.85	23.95	0.897
Systolic pressure 2	103	135.20	18.07	87	121.94	15.45	0.004
Diastolic pressure 2	103	83.70	14.67	87	77.01	11.83	0.065
Pulse 2	102	102.69	16.55	84	96.06	18.26	0.213
Med usage[f]	N	N on med	% on med	N	N on med	% on med	
Labetalol	105	37	35.2	89	22	24.7	0.110
Ketorolac	105	22	21.0	89	17	19.1	0.720
Ondansetron	105	22	21.0	89	17	19.1	0.726
Esmolol	105	6	5.7	89	2	2.3	0.242

[a] Comparison outcomes and measures by study drug using repeated measures longitudinal models. Means are overall across all treatments; *p*-values also take into account variability across treatments and within subject.
[b] Refers to number of concomitant psychotropic drugs per patient; *N* refers to number of patients given each anesthetic drug.
[c] *N* refers to total number of observations per analysis. For "Total Meds," this refers to number of patients randomized to each anesthetic group. For all other analyses, it refers to total number of treatments with that anesthetic medication. The numbers vary due to some patients' not receiving all six study treatments and to missing data.
[d] Refers to number of minutes spent in the ECT suite prior to transfer to the recovery area.
[e] For blood pressure and heart rate data, "1" refers to just before transfer to recovery, and "2" refers to end of recovery.
[f] "Med usage" here refers to adjunctive anesthesia medications.

against possible psychotomimetic side effects of ketamine. Further research is warranted.

There has been interest in using ketamine in ECT anesthesia as a way of possibly blocking ECT-induced cognitive dysfunction. In the Krystal et al. (2003) ketamine case series, time to re-orientation after the ECT seizures was shorter with ketamine than with methohexital. However, in the McInnes and James, 1972 and Orecchia et al., 1969 case series, time to re-orientation was reported to be longer with ketamine than with methohexital. Loo et al. (2012), utilizing an extensive battery of neuropsychological tests in their randomized trial, found no cognitive advantage of adding ketamine to thiopental anesthesia. McDaniel et al. (2006) randomized ECT patients to anesthesia with either ketamine 1.0 mg/kg or etomidate 0.3 mg/kg and found less decline in word list recall after six ECT treatments in the ketamine-treated group. However, that study involved a very small sample size (N=five for each group).

We found no advantage of ketamine over methohexital in recovery room parameters. Motor seizure lengths were longer with ketamine. Systolic pressures were higher with ketamine than with methohexital. Interestingly, some older open-label case series utilizing ketamine as ECT anesthetic have found no particular advantages with it (Rasmussen et al., 1996; Orecchia et al., 1969; McInnes and James, 1972; Brewer et al., 1972), although Krystal et al. (2003) did find that switching to ketamine anesthesia caused a prolongation of seizure length.

There are several limitations in this study. The use of depression self-report scales may be criticized. We used self-report scales because we did not have one consistent person available to perform clinician-administered scales, nor did we have the resources to establish good inter-rater reliability among a group of raters. However, the validity of the HADS has been established (Zigmond and Snaith, 1983). Also, the HADS has been shown to correlate well with clinician-administered rating scales (Bunevicius et al., 2012; Castelli et al., 2009; Laux et al., 2013). Thus, we believe it is unlikely that clinician-administered scales would have changed our results. Another limitation is that there were two electrode placements used, but the distribution of unilateral and bilateral was the same in both groups, so this was unlikely to be a significant confound. Similarly, stimulus dosage was not significantly different between the two groups, and dosing scheme (six times threshold for unilateral and 1.5 times threshold for bitemporal) was the same regardless of anesthetic drug. Concomitant psychotropics were not controlled and were determined by the choice of the primary treating psychiatrists. However, as seen in the table, there was no significant difference in number of such medications used between the two groups. Additionally, there were missing data due mainly to patients' not receiving 6 study treatments and in a few cases to the wrong study anesthetic being used, as indicated above. Finally, the assessment of the cognitive outcomes, which consisted of the MMSE and postictal orientation, are not as sensitive as in-depth neuropsychological testing.

In summary, we found that ketamine anesthesia was not associated with acceleration of the antidepressant effect of ECT,

nor was there a cognitive or recovery room benefit. Motor seizure duration was significantly higher with ketamine, and this may be a useful characteristic of this drug in situations where seizure duration with other anesthetic agents becomes unacceptably short.

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