A Randomized Pilot Study Comparing Ketamine and Methohexital Anesthesia for Electroconvulsive Therapy in Patients with Depression

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Abstract

Objective—This randomized controlled pilot study examines the differences in response to electroconvulsive therapy as defined by an improvement of depressive symptoms between ketamine and methohexital as the primary anesthetic agent. Side effects and cognitive tolerability were also examined.

Methods—Subjects undergoing electroconvulsive therapy for unipolar or bipolar depression were randomized to receive ketamine or methohexital as the anesthetic agent. Primary outcome measure includes the Hamilton Rating Scale for Depression (17-item). Secondary outcome measures included Mini-Mental Status Examination (MMSE) and Beck Depression Inventory. All ratings were conducted masked to anesthetic agent. Due to multiple outcome measures obtained over time, mixed models were used to account for the correlations among the measurements within the subjects. Since outcomes were either normally distributed or approximately normally distributed, general linear mixed models were fit with a random intercept specified.

Results—A total of 21 subjects were enrolled, and 16 were randomized (methohexital, n= 8; ketamine, n=8). The two treatment groups did not differ statistically in any demographic characteristic. No statistical difference was found between the ketamine and methohexital groups for an improvement in depressive symptoms (p=0.6); however, subjects in both groups showed

significant improvement in depression overtime (ketamine, p<0.0001; methohexital, p<0.0001). MMSE results did not differ between groups, and fatigue was reported more in subjects receiving ketamine (p=0.03).

Conclusion—The results of this pilot study are inconclusive as they lack power to support an advantage of ketamine anesthesia compared to methohexital in ameliorating depressive symptoms for electroconvulsive therapy.

INTRODUCTION

Electroconvulsive therapy (ECT) has been in use since 1938 and is one of the most effective and safe treatments for depression[1]. Researchers have made progress in optimizing ECT procedures to improve response and reduce side effects, and the choice of anesthetic agent has garnered attention. Any anesthetic agent used in ECT should have a short duration of action, and both methoxheital and ketamine satisfy this requirement. Methohexital is the gold standard anesthetic agent for use in ECT largely based on its minimal anticonvulsant properties. Agents, such as ketamine, have been used when a shortage of methohexital has occurred[2].

Ketamine is particularly useful in prolonging seizure duration in patients who experience a seizure duration less than 25 seconds with methohexital[3]. A more rapid improvement of depression symptoms with ketamine compared to thiopental[4,5] and propofol[6,7] anesthesia has been reported. In contrast, studies have found no difference in antidepressant outcomes between ketamine and methohexital[8], thiopental[9] and propofol[10] anesthesia. A meta-analysis of ketamine augmentation of ECT evaluated five trials (n=89) and found a statistically significant decrease in depressive symptoms after the initial treatment but no change in depressive symptoms at treatment closure[11]. When ketamine anesthesia is used in ECT, hypertensive[5,7] and cognitive side effects have been reported as well as post-ECT delirium[7] and disorientation and restlessness[10]. Ketamine has also been showed to be well-tolerated in multiple studies[3,4,12].

These comparative anesthetic studies supporting the use of ketamine in ECT parallel the investigations of intravenous ketamine infusions as a treatment for depression, particularly treatment refractory depression. In comparison to ketamine's use as an anesthetic agent, ketamine as an antidepressant is administered at half the dose and infused slowly over 40 minutes. Briefly, a single dose of intravenous ketamine acutely alleviates depressive symptoms[13,14], including suicidal ideation[15]. These antidepressant effects have also been shown with a repeated dose schedule that mimics an ECT schedule[16,17].

It is unclear if ketamine anesthesia in ECT would improve response and/or reduce side effects compared to other anesthetic options. This randomized controlled pilot study examines the differences in antidepressant response to ECT, defined by an improvement of depressive symptoms, between ketamine and methohexital as the primary anesthetic agent. We also examined side effects, including cognitive tolerability. We hypothesized that ketamine anesthesia would be well tolerated and result in a greater reduction in depressive symptoms compared to methohexital.

METHODS

The study was approved by the Institutional Review Board at the University of Arkansas for Medical Sciences (UAMS) prior to study initiation. Participants were recruited from the Psychiatric Research Institute at UAMS between July 2013 and August 2014. All subjects consented to ECT prior to being approached for study participation and gave informed consent prior to study initiation. Treatment decisions (e.g., adjunctive medications and continuation of ECT) were made by the treatment team and not influenced by study participation. Inclusion criteria included: 1) age 18 years, 2) a primary diagnosis of unipolar or bipolar depression per a Structured Clinical Interview for DSM-IV Disorders[18] (SCID), and 3) 17-item Hamilton Depression Rating Scale[19] (HAM-D) 20. Exclusion criteria included: 1) non-English speaking, 2) prior adverse event with ketamine or methohexital anesthesia, 3) current pregnancy, and 4) body mass index >40 due to concerns of appropriate anesthesia methods which are based on a measurement not available to study personnel. At enrollment, participants underwent a SCID, HAM-D, and Beck Depression Inventory[20] (BDI).

Electroconvulsive therapy was performed with MECTA spectrum 5000Q system and as routinely prescribed – three days a week. Randomization occurred using the 'urn' method to ketamine or methohexital anesthesia prior to the initial treatment. The treatment team, consisting of the attending psychiatrist and anesthesiologist administering ECT, were not blinded to the anesthetic agent; provided standard clinical care; and could override study protocol if in the patient's best interest. ECT was initiated with non-dominant unilateral electrode placement. Starting stimulus intensity was determined using the half-age method with subsequent increases made if patients had a motor seizure duration <25 seconds and/or EEG seizure activity <30s. If subjects failed to respond after stimulus dose increases, conversion to bilateral electrode placement was completed. Subjects underwent up to six ECT treatments in the study; however, additional treatments were allowed if determined to be clinically beneficial by the treatment team.

Intravenous induction of anesthesia was accomplished in the standard manner with 1% methohexital or 1% ketamine. For each anesthetic, a dose of 1 mg/kg body weight was administered as a bolus with subsequent titration to achieve sufficient anesthesia.

Two raters completed all assessments blinded to anesthetic agent. HAM-D and BDI were obtained 24–48 hours after each treatment, and extended follow-up via a phone interview was conducted at 7; 21; 60; and 90 days after final treatment. Side effects were coarsely measured using the Mini Mental Status Examination[21] (MMSE) prior to each treatment, and subjects were openly asked to report subjective side effects 24–48 hours after each treatment.

For each treatment, the treatment team recorded the following parameters: electrode placement, stimulation dose, anesthetic agent and dose, motor and EEG seizure duration, and adverse events. At study completion, study staff were unblinded and reviewed anesthesia and ECT records.

Primary outcome measure included HAM-D. Secondary outcomes measures included BDI and MMSE. Descriptive statistics for the baseline sample were calculated. Treatment response is defined a 50% decrease in baseline HAM-D score. Remission is defined as a HAM-D score 7. Due to multiple observations obtained over time, repeated measure analyses were used to account for the correlations among the measurements within the subjects. The outcomes were either normally distributed or approximately normally distributed, and general linear mixed models were fit with a random intercept specified. The dependent variables were HAM-D, BDI, and MMSE respectively and the independent variable was the group variable for ketamine vs. methohexital plus time variable indicating the number of the assessment. Electrical dose; motor seizure duration; and central seizure duration were compared between the groups using general linear mixed models. The interaction between the group variable and time was also tested in each model and excluded if not significant at .05 level. The number of individual ECT treatments was compared between the groups using two-sample T-test. Side effects between the groups were compared using Fisher exact test. Analysis was done using SAS 9.4.

RESULTS

The study enrolled 21 subjects and randomized 16. Subjects were withdrawn for the following reasons: concerns of ketamine anesthesia (n=2), completing ECT at another facility (n=1), not undergoing ECT treatment (n=1), and no reason given (n=1). All subjects initiated ECT as an inpatient in a psychiatric unit at the Psychiatric Research Institute. Six time points (i.e., baseline plus five follow-ups) were used as only six subjects completed study visits beyond this measure, including the extended follow-up appointments (7, 21, 60, and 90 days post 6th ECT treatment). Additionally, study results using all time points had similar results. Retention of study participants was difficult due to few patients having the social resources (e.g., transportation, financial, housing) to attend outpatient ECT.

Demographics, diagnoses, and depression and cognitive measures at baseline between the treatment groups did not differ statistically in any measure (Table 1). Of subjects with bipolar depression, three subjects in the methohexital group had bipolar I disorder; one subject in the ketamine group had bipolar I disorder; and one subject in the ketamine group had bipolar II disorder. Two subjects in the ketamine group had unipolar depression with psychosis. The subjects received 78 total ECT treatments, all with right unilateral electrode placement. Subjects received on average 4.9±1.3 treatments (range of 2–6). There was no significant difference in number of treatments (p=0.6); electrical dose (p=0.8); motor (p=0.8) seizure duration, or central (p=0.2) seizure duration between groups.

Table 2 displays the depressive and MMSE scores at baseline and at each post ECT treatment time point between the groups. No time by treatment group interaction was found to be significant for HAM-D, BDI, or MMSE. The group effect of ketamine vs. methohexital was not significant either for HAM-D (p=0.9), BDI (p=0.6), or MMSE (p=0.3). For HAM-D and BDI, both groups showed a response to ECT [p<0.0001 for all except post ECT #1 HAM-D (p=.01)].

Fatigue was reported more with ketamine (p=0.03). Of note, a subject receiving ketamine anesthesia had an episode of bradycardia noted in the fifth treatment that acutely resolved without incident.

DISCUSSION

The study results do not support an advantage of ketamine compared to methohexital anesthesia in ameliorating depressive symptoms or in cognitive tolerability; however, the results are underpowered to detect changes. The groups were comparable in demographic and psychiatric characteristics without any statistical difference between number of treatments, motor and central seizure duration, and electrical dosage utilized. Our findings are similar to reports comparing ketamine to methohexital[8], propofol[10], and thiopental[9].

Ketamine has been shown to provide cognitive advantages over other anesthetic agents used in ECT[4,5]. This study found no difference in cognitive side effects between ketamine and methohexital - a finding similar to other studies[3,8,12]. Fatigue was more commonly endorsed by subjects undergoing ketamine anesthesia. A self-limiting episode of bradycardia did occur in a subject who received ketamine anesthesia. Ketamine is known to cause a sympathomimetic response and is an unlikely cause for bradycardia.

An advantage to ketamine anesthesia in ECT is prolonged seizure duration; however, current data have shown mixed results. This study, like others[4,10,] did not find a significant difference in motor or central seizure duration between the groups. In contrast, prolonged seizure duration has been shown with ketamine compared to propofol[7] and thiopental[5]. Other studies showed only prolonged motor seizure duration with ketamine compared to methohexital[8] and ketamine plus thiopental[9]. Similarly, Okamoto et al[6] showed only longer central seizure duration in the first and sixth treatments.

The study has several strengths. The study utilized blinded raters as well as objective and subjective depression rating scales. Randomization procedure resulted in similar group characteristics with one exception, both subjects with psychotic depression were randomized to the ketamine group. This difference could have confounded the results; however, this is unlikely due to our small sample size.

Definitive conclusions are limited by the small sample size and inadequate power. The current study is smaller than those previously published[8]; however, any reportable data are useful given the scarcity of research on the subject. A higher than expected drop out rate is concerning secondary to a decreased number of subjects completing a standard ECT course of six treatments and an inability to delineate the long-term effects of ketamine anesthesia. Another limitation is the utilization of the MMSE to evaluate cognition. The MMSE was chosen based on its familiarity to the researchers and quick administration; however, it provides a coarse measure. Lastly, the study design allowed participants to receive more than six treatments if believed to be clinically beneficial. As the treatment team was not blinded to anesthetic agent, the treatment team may have had bias towards one of the treatment groups when making this decision.

With the growing evidence supporting the use of ketamine infusions in the treatment of treatment-resistant depression, it can be postulated that ketamine anesthesia may have added benefits in ECT. This pilot study does not support an antidepressive benefit of ketamine anesthesia in comparison to methohexital; however, findings are inconclusive given the inadequate power. Given the study limitations and need to optimize treatment of depression, further research is warranted.

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Table 1

Descriptive statistics

	Total (n=16)	Ketamine (n=8)	Methohexital (n=8)
Age (years, mean±sd)	40.9±14.1	43.6±14.6	38.1±13.9
Gender (n (%))			
Male	3 (18.8)	2 (25.0)	1 (12.5)
Female	13 (81.3)	6 (75.0)	7 (87.5)
Education (years, mean±sd)	13.1±2.7	13.0±2.1	13.1±3.3
SCID Diagnosis (%)			
Unipolar Depression	11 (68.8)	6 (75.0)	5 (62.5)
Bipolar Depression	5 (31.3)	2 (25.0)	3 (37.5)
Baseline Measures (mean±sd)			
BDI	35.0±7.6	34.0±4.5	36.0±10.0
HAM-D (17 Item)	26.6±4.0	27.4±5.0	25.8±2.7
MMSE	26.8±2.2	27.5±2.1	26.0±2.1
ECT Parameters (mean±sd)			
Number of Treatments	4.9±1.3	5.1±1.0	4.6±1.6
Electrical Dose	52.5±30.4	54.0±27.7	50.8±33.5
Motor Seizure Duration (seconds)	35.9±14.7	35.3±12.0	36.7±17.5
Central Seizure Duration (seconds)	65.7±41.2	55.5±22.2	77.8±54.0
Treatment Response (%)			
Responders	6 (37.5)	4 (50.0)	2 (25.0)
Remitters	1 (6.3)	1 (12.5)	0 (0.0)

Table 2

Outcome Measures (mean±sd)

Outcome	HAM-D		BDI		MMSE	
Group	Ketamine	Methohexital	Ketamine	Methohexital	Ketamine	Methohexital
Baseline	27.4±5.0	25.8±2.7	34.0±4.5	36.0±10.0	27.5±2.1	26.0±2.1
Post ECT #1	21.4±4.6	24.3±5.2	24.3±10.3	18.8±10.3	27.8±2.1	26.6 ±3.3
Post ECT #2	18.8±4.2	18.4±7.3	16.4±7.2	19.3±14.4	26.8±2.3	26.1±2.7
Post ECT #3	13.3±4.4	14.1±4.4	13.5±5.9	11.3±5.9	27.3±2.3	26.6±3.3
Post ECT #4	13.9±4.3	16.8±7.7	18.6±6.2	15.0±8.1	27.2±2.6	26.3±2.5
Post ECT #5	12.8±4.6	14.3±5.1	15.3±2.6	16.3±11.7	25.0 ±0.0	26.7 ±3.1