Journal of Affective Disorders 201 (2016) 124–130

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Mood and neuropsychological effects of different doses of ketamine in electroconvulsive therapy for treatment-resistant depression

Xiaomei Zhong, Hongbo He, Chunping Zhang, Zhijie Wang, Miaoling Jiang, Qirong Li, Minling Zhang, Xiong Huang *

The Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital), Guangzhou, China

ARTICLE INFO

Article history:
Received 3 November 2015
Received in revised form
10 April 2016
Accepted 11 May 2016
Available online 12 May 2016

ABSTRACT

Background: Treatment-resistant depression (TRD) is a growing clinical challenge. Electroconvulsive therapy (ECT) is an effective tool for TRD treatment. However, there remains a subset of patients who do not respond to this treatment with common anesthetic agent. Ketamine, a noteworthy anesthetic agent, has emerged as an augmentation to enhance the antidepressant efficacy of ECT. Trials of i.v. ketamine in TRD indicated dose-related mood enhancing efficacy. We aimed to explore anesthetic and subanesthetic concentrations of ketamine in ECT for TRD with respect to their impact on mood and neuropsychological effects.

Methods: Ninety TRD patients (36 males, 54 females; average age, 30.6 years old) were randomly assigned to receive either ketamine (0.8 mg/kg) (n=30), subanesthetic ketamine (0.5 mg/kg) plus propofol (0.5 mg/kg) (n=30) or propofol (0.8 mg/kg) (n=30) as an anesthetic and underwent 8 ECT sessions. The primary outcome measures were the 17-item Hamilton Depression Rating Scale (HDRS-17), cognitive assessments and seizure parameters.

Results: The ketamine group had an earlier improvement in HDRS-17, longer seizure duration, lower electric quantity, a higher remission rate, and a lower degree of executive cognitive impairment compared to the ketamine+propofol and propofol groups. The ketamine+propofol group showed earlier improvement in the HDRS-17, a longer seizure duration and a different seizure energy index when compared to the propofol group.

Limitations: The postoperative dissociative side effect was not assessed.

Conclusions: Both anesthetic and subanesthetic concentrations of ketamine have rapid mood enhancing actions in ECT for TRD, while anesthetic concentrations results in larger magnitudes of antidepression and cognitive protection. ECT with ketamine anesthesia might be an optimized therapy for patients with TRD.

1. Introduction

Major depressive disorder is a widespread psychiatric illness, affecting approximately 350 million people worldwide and leading to severe health and socioeconomic consequences (Oremus et al., 2015). Despite the growing selection of psychopharmacological treatments, only 60–70% of major depressive disorder patients will respond to first-line treatment with antidepressant drugs. Evidence indicates that at least one-third of patients with major depressive disorder do not reach clinical remission and become treatment resistant (Oremus et al., 2015). Treatment-resistant depression (TRD) is defined as the failure to respond to an adequate dosage and duration of at least two different therapeutic antidepressant drugs (Mathew, 2008). The treatment of TRD is challenging. Electroconvulsive therapy (ECT) is generally considered to be the most effective treatment for TRD (McGirr et al., 2015). ECT affects multiple central nervous system components by inducing a bilateral general seizure. Seizure duration and electric quantity are the two most critical parameters in ECT. There is evidence that adequate seizure duration is necessary for antidepressant effects, and higher electric doses hasten the clinical response (Boylan et al., 2000). However, the response rate of ECT using a common anesthetic agent (such as propofol, thiopental and etomidate) is approximately 50–60% (Shelton et al., 2010). This result has stimulated interest in augmentation strategies that aim to increase the effectiveness of ECT for TRD treatment (McGirr et al., 2015).

* Corresponding author.
E-mail address: 1968hxiong@163.com (X. Huang).

http://dx.doi.org/10.1016/j.jad.2016.05.011
0165-0327/

Ketamine, an N-methyl-D-aspartate (NMDA) receptor blocking agent, has emerged as a novel, rapid-acting antidepressant, and even when administered in low-doses intravenously, ketamine can rapidly reduce depressive symptoms and suicidal ideation in patients with affective disorders (Naughton et al., 2014). A growing body of research demonstrates that the glutamatergic system plays an important role in the pathophysiology of major depression and the mechanism of antidepressant effects. The rapid antidepressant effect of ketamine is due to the activation of the mammalian target of rapamycin (mTOR) signaling pathway together with the inhibitory phosphorylation of eukaryotic elongation factor 2 (eEF2) and glycogen synthase kinase-3 (GSK-) (Gideons et al., 2014). Ketamine is a noteworthy anesthetic agent used mainly for starting and maintaining anesthesia. Because of its anesthetic antidepressant effects, ketamine has emerged as a putative augmentation agent to enhance the antidepressant efficacy of ECT (Valentine et al., 2011; Wang et al., 2012; Yalcin et al., 2012; Jarventausta et al., 2013; Kucuk et al., 2013; Bryson et al., 2014; Rasmussen et al., 2014; Erdil et al., 2015; Sartorius et al., 2015). An increasing number of studies have tested the antidepressive effects of ketamine for ECT anesthesia in medication-free or antidepressant-antipsychotic drug combinations in patients with MDD or TRD (McGirr et al., 2015), while studies of intravenous ketamine without ECT were often performed in TRD patients or the ECT-resistant group (Serafini et al., 2014). Most studies of repeated-dose intravenous ketamine for TRD demonstrated rapid antidepressant effects (Serafini et al., 2014). However, the efficacy results of ketamine for ECT anesthesia are inconsistent. Some studies reported a lack of clinical efficacy and some confirmed its efficacy in improving depressive symptomatology earlier when using ketamine as an anesthesia agent or an adjunctive agent to ECT compared with propofol, thiopental or methohexital anesthesia (Okamoto et al., 2010; Abdallah et al., 2012; Loo et al., 2012; Wang et al., 2012; Jarventausta et al., 2013; Rasmussen et al., 2014). Further studies are needed to provide evidence regarding this issue.

A previous study of ketamine administered with anesthetic concentrations as augmentation in ECT for TRD indicated an increased effect (Okamoto et al., 2010), while subanesthetic concentrations showed no effect (Jarventausta et al., 2013). These studies suggest that the antidepressant efficacy may be influenced by the dose of ketamine used in ECT. The trial of intravenous injection (i.v.) ketamine in TRD patients provided evidence that increasing doses of ketamine produced more marked and more sustained antidepressant responses (Lai et al., 2014). To our knowledge, there is no study comparing the antidepressant effect of ketamine alone (anesthetic concentration) and subanesthetic ketamine as an anaesthic induction for ECT in TRD treatment. The optimal mode of ketamine anesthesia for ECT remains unknown.

In additional, cognitive impairment is common after ECT. The use of ECT is limited due to its adverse effects on cognitive function. Patients experience disorientation after each treatment and may have anterograde amnesia after the ECT course (Moscrip et al., 2004). Excitotoxic damage related to excessive glutamatergic transmission through the NMDA receptor during ECT is a postulated molecular mechanism for cognitive impairment (Loo et al., 2012). When ketamine is used in anesthetic doses, it exerts neuroprotection by inhibiting the NMDA-receptor activation, mediating beneficial changes in apoptosis-regulating proteins, and interfering with the inflammatory response to injury (Hudetz and Pagel, 2010). Ketamine as an anesthesia for ECT may exhibit potential cognitive protection.

The aim of the present study was to compare the effects of ketamine, the subanesthetic ketamine/propofol combination (ketamine+propofol) and propofol as anesthesia on the antidepressant efficacies, ECT parameters, cognitive protection and side effects in patients with TRD.

2. Materials and methods

2.1. Subjects

The study was approved by the ethics committee of the Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital). Written informed consent was obtained from all participants. All patients were recruited from the wards of the Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital). The ECT sessions were performed in the Department of ECT of The Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital). Patients with TRD were enrolled between April 2011 and April 2014. All patients fulfilled the diagnostic criteria for major depression or bipolar disorder with a current major depressive episode according to the ICD-10 diagnostic criteria and had no clinical response to at least two antidepressant drugs of different pharmacological classes at adequate dosages for at least 6 weeks for their current depression episode. The exclusion criteria were as follows: the existence of a mental disorder other than major depression or bipolar disorder with a current major depressive episode, such as schizophrenia and dementia; a history of seizures; a history of substance abuse including alcohol or drug abuse; pregnancy; the presence of neurological disorders or traumatic brain injury; the presence of any serious physical disease, such as intracranial hypertension, cerebrovascular disorder, respiratory tract disease; and other contraindications for ECT or anesthesia.

2.2. Research intervention

TRD patients were randomized to receive ketamine, ketamine+propofol or propofol as anesthesia. Both the rater and the patients were blind to the anesthetic agent. ECT treatment was performed three times per week for three consecutive weeks for a total of eight treatments. No antipsychotic or antidepressive drugs were prescribed to the patients during the period of ECT. All three groups first received atropine sulfate (1 mg). Then, they received ketamine (0.8 mg/kg), ketamine (0.5 mg/kg) plus propofol (0.5 mg/kg) and propofol (0.8 mg/kg) I.V. push for anesthesia for the ketamine, ketamine+propofol and propofol groups, respectively. Succinylcholine (1 mg/kg) was administered intravenously as a muscle relaxant after the induction of anesthesia.

Bitemporal ECT was performed using the Thymatron ® IV device (Somatics LLC, Lake Bluff, Illinois, USA). The seizure threshold was determined using the half-age method (% energy=half the age) in each case. Seizure duration and the seizure energy index on the EEG were recorded during anesthesia. Systolic and diastolic blood pressures were recorded just before anesthesia and 10 min after the ECT procedure.

2.3. Psychopathology and cognitive assessment

The 17-item Hamilton Depression Rating Scale (HDRS-17) was used to assess the severity of depressive symptoms and the treatment response. The antidepressant response was defined at a $\geq$ 50% reduction in the HDRS-17 total score from baseline, and remission was considered a HDRS-17 score $\leq$ 7. The 18-item Brief Psychiatric Rating Scale (BPRS-18) was used to evaluate general psychopathology symptoms. These two scales were administered at baseline and after treatments one, two, three, four and six on the mornings of the next scheduled ECT and 48–72 h after the last (eight) treatments.

The Word Fluency Test, the Digit Symbol Test, the Digit Span test, the Wisconsin Card Sorting test, the Tower of Hanoi, the Trail Making Test and the Visual Regeneration Test were used to assess cognition at baseline and 48–72 h after the eighth treatment. All of