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Chapter

# Ketamine Anesthesia in Electroconvulsive Therapy

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## Abstract

Electroconvulsive therapy (ECT) is highly effective both Major Depressive Disorder (MDD) and Bipolar Disorder (BD). Ketamine, an antagonist of the N-Methyl-D-aspartate receptor, has been described to have antidepressant properties. There is a hypothesis that ECT performed with anesthesia using ketamine is more effective than conventional ECT. Also, although ECT is the gold standard for BD and MDD, there are questions about which is more effective, ketamine treatment or ECT, and whether ketamine is more effective when used in combination with ECT. In this chapter, we review the current literature on the effectiveness of ECT and ketamine. Furthermore, we discuss whether ketamine can be an alternative treatment to ECT for patients with TRD.

**Keywords:** ketamine, electroconvulsive therapy, depression, side effect, cognitive impairment

## 1. Introduction

Major Depressive Disorder (MDD) and Bipolar Disorder (BD) are very popular psychiatric disorders that affect 10–15% of people in their lifetime. If symptoms do not improve during episodes of depression with at least two types of antidepressants, this condition is referred to as Treatment-Resistant Depression (TRD), which is observed in 12–20% of patients with depression [1]. The gold standard treatment for TRD is Electroconvulsive Therapy (ECT) [2]. ECT is a safe and effective treatment for TRD. Data shows that the efficacy rate is 79%, and the remission rate is 75% when ECT is used for patients with MDD [3]. Various oral treatments have been introduced since the 1990s. Tricyclic and tetracyclic antidepressants had emerged by the 1990s, and second-generation antidepressants such as selective serotonin reuptake inhibitors (SSRI) and serotonin-noradrenaline reuptake inhibitors (SNRI) were introduced at the end of the 1990s. Although the cause of depression is not clear, the monoamine hypothesis attributes depression to a decrease in neurotransmitters such as serotonin and noradrenaline, which are monoamines, and the action mechanism of the antidepressants is often explained based on the monoamine hypothesis. SSRI and SNRI have fewer side effects, such as dry mouth and dysuria, compared with tricyclic antidepressants, and internationally, they are recognized as the standard treatment. However, the availability of many antidepressants does not necessarily mean that the drug therapy for depression is adequate. STAR*D [4], a large-scale clinical trial investigating the efficacy of switching to the next stage of treatment in patients with depression showing inadequate response to antidepressant medication, found that about half of the total population responded

to the initial SSRI treatment, with one-third achieving remission; the response and remission rates decreased with each switch to a different treatment.

Remission has been pointed out to be related to social functioning and prognosis, which is emphasized [5] as a therapeutic goal of depression treatment. According to the results of STAR*D [4], the cumulative remission rate is approximately 67% when medication is switched thrice. This finding suggests that a certain number of patients do not show an adequate response even after treatment with multiple antidepressants, and the limited efficacy of standard treatments is a clinical problem.

## 2. What is ECT?

Electroconvulsive therapy (ECT) is a treatment method in which generalized seizure activity is induced in the brain through electrical stimulation, producing neurobiological effects to improve clinical symptoms. The history of ECT can be traced back to 1938 when Cerletti U and Bini L of Italy developed a method to induce seizures by passing an electric current through the brain from the scalp on the head, which was the beginning of ECT. Since then, ECT has spread rapidly. Earlier in ECT, an electric current was passed without pretreatment, such as intravenous anesthesia, causing generalized tonic-clonic seizures, feeling of extreme fear experienced by patients, and side effects such as bone fractures or dislocations due to seizures were the problems posed by the treatment. For this reason, ECT was developed, in the 1950s, to pass an electric current without causing seizures of skeletal muscles by keeping patients on mechanical ventilation and administering a combination of anesthetics and muscle relaxants under the supervision of an anesthesiologist.

## 3. Indications for ECT

ECT is said to have no absolute contraindications. Relative contraindications include (1) intracranial lesions, (2) increased intracranial pressure, (3) recent myocardial infarction, (4) recent cerebral infarction, (5) unstable aneurysm or vascular malformation, (6) pheochromocytoma, and (7) patients with poor physical condition (physical status of 4 or 5 as per the American Society of Anesthesiologists, i.e., with severe threatening systemic disease or moribund). Although medical history interview (allergies, asthma, and history of surgery), blood biochemical tests, electrocardiogram, chest and abdominal X-rays, head CT, and electroencephalogram are performed and recorded before ECT, an echocardiogram, head MRI, and MRA should also be conducted. The cognitive function should also be evaluated in advance, as postictal delirium and transient cognitive impairment may occur, which are described later. ECT is indicated for psychiatric disorders such as depression, schizophrenia, and mania, and has also been shown to be effective in treating Parkinson's disease, malignant syndromes, and chronic pain. The effectiveness of ECT differs depending on the subtype of schizophrenia. At the same time, the treatment is effective for catatonic and acute onset paranoia cases, and there is little effect in hebephrenic and chronic cases. The primary use of ECT should be considered in the following situations: (1) severe symptoms, such as the high risk of suicide attempt or extreme agitation; (2) general deterioration of the patient's condition due to psychiatric symptoms, such as refusing food or catatonic condition; (3) high risk of other forms of treatment, such as in the case of elderly patients or pregnant women; (4) history of ECT treatment with a favorable response; and

(5) preference of the patient. The secondary use of ECT may be considered when the patient is resistant to drug therapy or the patient's tolerability to drug therapy is poor. The indication for ECT is determined based on a combination of diagnosis, symptom type, severity, treatment history, consideration of the expected risks and benefits of ECT with other treatments, and patient's preference.

## 4. Side effects of ECT

The most common side effects of ECT are postictal delirium and transient cognitive impairment. However, the stimulation dose can be adjusted according to the seizure threshold of each patient by using pulse wave therapy devices, which has significantly reduced seizures compared with conventional treatments. Although the parasympathetic nervous system is dominant immediately after an electric current is passed during ECT, the sympathetic nervous system subsequently becomes dominant. Therefore, bradycardia and sinus arrest may temporarily occur early on. Thereafter, tachycardia and elevated blood pressure are observed, and ventricular arrhythmias may also occur. Although tachycardia and elevated blood pressure are transient, patients with a history of hypertension or ischemic heart disease should be intravenously administered antihypertensive drugs. Even with using muscle relaxants in ECT, the masseter muscle contracts when an electric current passes and can damage the teeth and oral cavity. Although dentures are removed to prevent this, and a bite block is used, dental treatment may be required before ECT if the teeth shake significantly. Other side effects include headache, myalgia, nausea, and prolonged convulsions. Manic episodes may also occur in bipolar depression.

## 5. Procedure of ECT

ECT is performed in the operating theater under respiratory and circulatory management by an anesthesiologist. In addition to stimulation electrodes and Electroencephalogram (EEG) electrodes (two channels on the left and right) attached to the forehead, Electrocardiogram (ECG) electrodes and Electromyography (EMG) electrodes (on the dorsum of one foot) are attached, the vital signs of the patient are checked, and intravenous anesthesia is administered. When the patient falls asleep, the blood flow to the lower leg with the EMG electrodes is restricted by applying a pressure equal to or more than the systolic blood pressure using the manchette of a sphygmomanometer and a muscle relaxant is administered intravenously. After muscle relaxation is confirmed, a bite block is inserted in the patient's mouth. After passing an electric current, tonic-clonic seizures are observed only in the lower leg with restricted blood flow. The bag-valve-mask ventilation is used when the patient falls asleep until it is confirmed that the patient has resumed spontaneous breathing. The vital signs are rechecked after the patient is fully awake and taken out from the operating theater. Even after returning to the ward, a monitor is attached to the patient for around 1 hour to check the vital signs. This procedure is performed 2–3 times a week, for a total of 8–12 times.

## 6. Drugs commonly used in ECT

Short-acting intravenous anesthetics are used. Propofol and thiopental are commonly used. The higher the dose of the anesthetic drug, the less likely that seizures will occur; hence, the minimum dose of the intravenous anesthetic drug that puts

the patient to sleep is administered. The muscle relaxant used is succinylcholine, which is a depolarizing muscle relaxant. Although non-depolarizing muscle relaxants may also be used to reduce myalgia and increased intragastric pressure, their long duration of action may lead to problems such as the need for a muscle relaxant antagonist [6] after ECT and residual muscle relaxation. Anesthesiologists are also aware that hyperventilation can lead to seizures.

## 7. Information on ketamine

Although ketamine is an old N-methyl-D-aspartate (NMDA) receptor antagonist, in recent years, the use of subanesthetic doses of ketamine as a therapeutic agent has been reported to have antidepressant effects. Some reports indicate remission rates exceeding 80% with the use of low doses of ketamine [7–10]. There have also been reports that the response to seizures was good when used as an adjunct to ECT, so we did a comprehensive study of the reports. Ketamine may be used independently or as an adjunct, in addition to propofol or thiopental.

We have cited reference Jankauskas et al., [11], which includes a summary up to 2017. Most studies show that when ketamine is used independently or in combination with non-barbiturates such as propofol at doses of 0.8 mg/kg or more during ECT, there is a faster improvement in symptoms and a significant improvement in depressive symptoms compared with the control group where ketamine is not used [12–16]. Seizures during ECT are longer in the intravenous anesthesia group with ketamine or ketamine alone than the intravenous anesthesia group without ketamine [14, 17, 18]. Ketamine was observed to significantly improve cognitive function in the original cases of cognitive decline [14]. Some results show a faster recovery in the ketamine group even if there is no change in the outcome [14, 19].

On the other hand, even if ketamine prolongs the duration of seizures, according to some reports, ketamine is not better than other anesthetics in reducing depressive symptoms or improving cognition [16, 20–23]. The effect of ketamine on the duration of seizures during ECT has been evaluated differently in each study, and the ECT protocols vary from institution to institution making efficacy assessment difficult [11]. The additional problem is that the assessment items (seizure duration, early stage of rapport, or cognitive improvement) do not match.

Since propofol suppresses the disadvantages of ketamine such as agitation, cardiotoxicity, nausea, and psychotomimetic effects, the combination of propofol and ketamine is good as propofol suppresses the disadvantages of ketamine without compromising its efficacy [13, 17]. Ketamine also reduces hypotension, a side effect of propofol, another reason for considering the combination as good [17]. Many reports indicate that the benefits of ketamine are not effective when used in combination with barbiturates due to the anti-seizure action of barbiturates and did not show a reduction effect for depression [12, 16, 20, 24].

Safety concerns with ECT include high rates of hypertension, prolonged QTc interval, transient arrhythmias, confusion or fear, and hallucinations that may occur upon awakening from the anesthetic [12, 13, 17, 20, 25–27]. The incidence of hallucinations has a positive correlation with the increase in ketamine dose, especially in the dose range of 0.8–2.0 mg/kg [13, 17, 20, 25–27]. Caution should be exercised when using ketamine in patients with cardiovascular diseases, as the drug increases blood pressure. Caution should also be exercised when using ketamine in patients with a history of psychomimetic episodes, as there is a possibility of psychotogenesis.

Concomitant use of propofol may be considered to mitigate some of these adverse effects [13]. However, the complexity and cost of the medication will

increase. Most of the adverse effects such as agitation, cardiotoxicity, nausea, and psychotomimetic effects are temporary [12, 16]. Therefore, an analysis of individual risks and benefits needs to be considered.

## 8. Role of ketamine in ECT in recent years

Although studies of varying scales and assessment have continued, some studies have found the addition of ketamine to ECT to be effective [28, 29], and some have found the addition as not effective [30]. We will introduce one such study. A multi-site randomized, placebo-controlled, double-blind trial, "Ketamine-ECT study" was planned at the University of Newcastle in the United Kingdom to investigate whether the adjunctive use of ketamine can attenuate the cognitive impairment caused by ECT [31]. ECT continues to be the gold standard for severe and treatment-resistant depression. However, a significant limitation contributing to the declining use of ECT is its association with cognitive impairment, especially in anterograde and retrograde memory and functional impairment.

On the other hand, preliminary data suggest that ketamine, used either as the sole anesthetic drug or in addition to other anesthetics, may reduce or prevent cognitive impairment after ECT. A hypothesis has been postulated that ketamine protects from excess excitatory neurotransmitter stimulation during ECT through glutamate receptor antagonism. The primary aim of the "ketamine-ECT study" was to investigate whether the adjunctive use of ketamine can attenuate the cognitive impairment caused by ECT. The secondary aim was to examine if ketamine increases the speed of clinical improvement with ECT. The summary of the study is that moderately to severely depressed patients who had been prescribed ECT were randomly grouped on a 1:1 basis to receive either adjunctive ketamine or saline in addition to standard anesthesia for ECT. A 0.5 mg/kg dose of ketamine was administered as a bolus instead of continuous administration. The primary neuropsychological outcome is anterograde verbal memory (Hopkins Verbal Learning Test-Revised delayed recall task) after four ECT treatments. Secondary cognitive outcomes include verbal fluency, autobiographical memory, visuospatial memory, and digitization span. Efficacy was assessed using evaluation by observer and report of subjects on the depressive symptoms by patients.

This randomized trial validated the hypothesis that low doses of ketamine administered with a course of ECT treatment would improve outcomes in depression. We did not find significant evidence for cognitive and efficacy outcomes by administering a dose of 0.5 mg/kg ketamine as an adjunct in patients treated with ECT for depression.

However, the number of subjects was less than the number of patients recruited, which implies that the small to medium benefits and medium to extensive harms of ketamine cannot be ruled out. Therefore, it is not always possible to conclude based on only these results. It is also debated that evaluation in this field is complicated, especially the evaluation of cognitive function after ECT. For example, although patients recover most of the cognitive decline after ECT within a few days to a few weeks after the completion of treatment, it is challenging to accurately measure the recovery of retrograde autobiographical memory, which is the primary concern for patients. Although this paper has been discussed extensively, the study did not indicate that ketamine improved the outcome of depression. However, since treatment-resistant depression still exists and some papers have shown that ketamine is effective, we believe it is worth continuing research by evaluating various subgroups or using an optimal psychological index to determine the efficacy.

## 9. Future of ketamine in ECT

As introduced in Section 8, there are more than 130 papers on the adjunctive use of ketamine with ECT; however, only a few are definitive. Although well-conceived studies with sufficient resources are needed, they are not conducted, and the availability of funding is also not likely. Many papers have recognized the efficacy of ketamine with small-scale studies. ECT is an effective treatment method in clinical practice since patients showing resistance to treatment with only oral medication are high at 33%. Memory impairment caused by ECT is a significant problem faced by patients. The condition of patients with depression before ECT treatment varies widely; hence, it is necessary to divide them into subgroups. If there is a possibility that ECT can improve cognitive impairment, we consider that further studies are needed to evaluate the effects of ketamine by dividing patients into more specific subgroups.

## 10. Ketamine as an alternative to ECT

As described in Section 8, the decline in cognitive function after the ECT procedure causes significant distress to patients [32]. Unfortunately, additional ECT is sometimes required due to the frequent recurrence of TRD. The recurrence rate of TRD within 6 months of ECT is reported to be between 39% (with continued medication) and 84% (without continued medication) [33]. If patients become aware of their cognitive impairment even once, ECT treatment becomes unbearably painful for them [33]. There is a pressing need to develop a treatment with the same effectiveness as ECT but with fewer side effects and recurrences. Ketamine, an NMDA receptor antagonist, has repeatedly shown an immediate and strong antidepressant effect in patients with MDD [34, 35]. Ketamine demonstrates a positive effect even in patients with severe TRD [36]. Whether ketamine can be an alternative treatment to ECT for patients with TRD is discussed in this section. There are six papers at present [37]. While randomized control trials [38–40] are discussed in three papers, the other three cover open-label trials [41–43]. The results suggest that ketamine therapy develops antidepressant effects more quickly than ECT, but perhaps the effect is not sustained compared with ECT. Unlike ECT, cognitive impairment was found to be less with ketamine therapy. The sample size of the studies was limited, followed different treatment protocols, and long-term follow-up was lacking in most trials. The occurrence of assignment bias is high as the trials were not randomized, and performing ECT and ketamine therapy in double-blind trials is difficult. The results of the current studies do not provide convincing evidence to indicate that ketamine therapy is an equally effective alternative to ECT for patients with TRD. If ketamine is used in high doses for chronic cases because of its advantages over ECT during treatment at the initial stage, it may cause memory impairment [44]. Long-term maintenance therapy with ketamine may make patients prone to ketamine-related addiction. This risk should be considered when comparing ketamine therapy to ECT. The reported acute side effects of ketamine therapy are dizziness, headache, blurred vision, body numbness, depersonalization, vertigo, double vision, and nausea. The reasons for discontinuing ketamine were dissociative symptoms, hypertension, and unpleasant experience. The impact of acute and chronic adverse events attributable to ketamine therapy needs to be compared with the common side effects of ECT treatment, such as cognitive impairment, myalgia, arthralgia, headache, and risks associated with general anesthesia. Studies with larger sample sizes and longer follow-up duration are needed.

## 11. Conclusions

ECT is still the gold standard for severe and treatment-resistant depression patients, but cognitive dysfunction after ECT is the problem. Although the antidepressant effect of ketamine has been attracting attention in recent years, it cannot be said that ketamine is an effective treatment alternative to ECT at this stage. Many studies have shown that adding small amounts of ketamine during ECT is effective with small-scale studies. Although well-conceived studies with sufficient resources are needed, they are not conducted.

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## Conflict of interest

The author declares no conflict of interest.

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