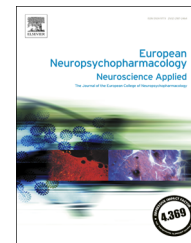




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Significant treatment effect of add-on ketamine anesthesia in electroconvulsive therapy in depressive patients: A meta-analysis



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Abbreviations: ECT, electroconvulsive therapy; CI, confidence interval; MA, meta-analysis; Tx, treatment; No., number; EEG, electroencephalogram; NMDA, N-methyl-D-aspartate; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF, brain-derived neurotrophic factor; BD, Bipolar depression; MDD, major depressive disorder; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text-Revision; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DSM-III, Diagnostic and Statistical Manual of Mental Disorders, 3rd edition; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, Revision; n/a, not available; MDD, major depressive disorder; SEM, standard error of mean; HAM-D, Hamilton Depression Scale; PHQ-9, Patient Health Questionnaire 9; HADS, Hospital Anxiety and Depression Scale; BDI, Beck Depression Inventory; MADRS, Montgomery-Åsberg Depression Rating Scale; USA, United States; ES, effect size; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; SD, standard deviation; BMI, body mass index; EMG, electromyography.

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Abstract

Add-on ketamine anesthesia in electroconvulsive therapy (ECT) has been studied in depressive patients in several clinical trials with inconclusive findings. Two most recent meta-analyses reported insignificant findings with regards to the treatment effect of add-on ketamine anesthesia in ECT in depressive patients. The aim of this study is to update the current evidence and investigate the role of add-on ketamine anesthesia in ECT in depressive patients via a systematic review and meta-analysis. We performed a thorough literature search of the PubMed and ScienceDirect databases, and extracted all relevant clinical variables to compare the antidepressive outcomes between add-on ketamine anesthesia and other anesthetics in ECT. Total 16 articles with 346 patients receiving add-on ketamine anesthesia in ECT and 329 controls were recruited. We found that the antidepressive treatment effect of add-on ketamine anesthesia in ECT in depressive patients was significantly higher than that of other anesthetics ($p < 0.001$). This significance persisted in both short-term (1-2 weeks) and moderate-term (3-4 weeks) treatment courses (all $p < 0.05$). However, the side effect profiles and recovery time profiles were significantly worse in add-on ketamine anesthesia group than in control group. Our meta-analysis highlights the significantly higher antidepressive treatment effect of add-on ketamine in depressive patients receiving ECT compared to other anesthetics. However, clinicians need to take undesirable side effects into consideration when using add-on ketamine anesthesia in ECT in depressive patients.

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1. Introduction

Electroconvulsive therapy (ECT) is a widely-used treatment for severe or refractory major depressive disorder (MDD) and bipolar depression (BD), and it has been reported to result in improvement rates ranging from 70% to 90% (Kho et al., 2003). Various anesthetic regimens have been utilized in ECT practice, including methohexital, propofol and thiopental.

Ketamine is a N-methyl-D-aspartate (NMDA) antagonist, and it was shown to have a neuroprotective effect in an animal study, which was possibly related to NMDA antagonism and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor activation (Brunson et al., 2001). In addition, recent trials have suggested that ketamine exerts an antidepressant effect through mechanisms involving NMDA receptor antagonists (Autry et al., 2011), activity at sigma receptors (Robson et al., 2012), and effects within the dopaminergic (Belujon and Grace, 2014) or serotonergic systems (Yamamoto et al., 2013). Furthermore, in addition to the therapeutic effects on specific receptors, ketamine has also been reported to play an important role in moderating the synthesis of important neurotrophic factors, such as increasing the secretion of brain-derived neurotrophic factor (BDNF) (Allen et al., 2015), and assisting in neuroplasticity and inflammatory modulation processes (Clarke et al., 2016). Taken together, these findings support the antidepressant effect of ketamine.

Despite the risk of undesirable side effects (Strayer and Nelson, 2008), clinical trials have shown the effect of ketamine in the treatment of acute unipolar or bipolar depression (Reinstatler and Youssef, 2015). Ketamine infusion provides a rapid therapeutic response in patients suffered from treatment-resistant depression (Abdallah et al., 2015). Two National Institute of Mental Health-funded cross-over studies reported greater improvements

in Montgomery-Åsberg Depression Rating Scale (MADRS) scores that were evident by 40 min and persisted for three more days compared with a placebo among patients with non-psychotic bipolar depression resistant to open antidepressants or mood stabilizers, and response rates at all time points (Diazgranados et al., 2010; Zarate et al., 2012). Furthermore, a recent meta-analysis confirmed the efficacy of the treatment effect of ketamine in depression with short term usage, but not in medium- or long-term usage (Fond et al., 2014). In addition, another study reported a relapse rate of depression of nearly 90% at 4 weeks after serial ketamine infusion as monotherapy (Shiroma et al., 2014). Furthermore, as a Schedule III controlled substance, ketamine must be used cautiously for medical application with regards to the risks of addiction or toxicity to the urinary tract (Bokor and Anderson, 2014). Therefore, the clinical applicability of ketamine monotherapy to treat depression seems to be limited.

On the other hand, because ketamine can be used as an anesthetic, some clinicians have prescribed it as an add-on anesthetic during ECT in depressive patients. Due to the rapid anti-depressant effect of ketamine (Diazgranados et al., 2010), early improvements in depression could be expected with add-on ketamine therapy in ECT, which may in turn be beneficial in shortening the hospital stay and hasten recovery from depression. Recent clinical trials have shown better efficacy using add-on ketamine in ECT than other anesthetics (Abdallah et al., 2012; Kranaster et al., 2011; Salehi et al., 2015; Wang et al., 2012); however other studies have reported contrasting results (Jarventausta et al., 2013; Loo et al., 2012; Rybakowski et al., 2016; Yoosefi et al., 2014). These inconsistencies may be due to differences in study design (Jarventausta et al., 2013; Wang et al., 2012), sites where ECT was applied (Kranaster et al., 2011; Rybakowski et al., 2016), or treatment course (Abdallah et al., 2012; Yoosefi et al., 2014).

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