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The use of ketamine in electroconvulsive therapy

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Summary

In recent years, data on the possibility of rapid clinical improvement after administration of ketamine in patients diagnosed with depression have been published more frequently. Ketamine, used as an anaesthetic during ECT procedures, despite earlier concerns, has both: a good safety profile and minimal effect on seizure threshold, which is used in cases of non-response to ECT. Postulated action of ketamine causes a rapid resolution of depressive symptoms and raised hopes to accelerate therapeutic effect of ECT in patients with severe depression, but studies provide contradictory data pointing to brevity of the observed effect. Studies examining the use of ketamine combined with other anaesthetic drugs emphasised not only its antidepressant effect, but also improvement in hemodynamic parameters during ECT treatment. The aim of this work on one hand is to make psychiatrists aware that the role of anaesthesiologist at ECT is not limited to anaesthetise a patient and provide muscle relaxation, and, on the other hand, to make anaesthesiologists aware that drugs they use have a significant effect on seizure parameters and indirectly on the effectiveness of ECT. Due to small size of studied populations the issue of antidepressant efficacy of ketamine requires further exploration.

Key words: ketamine, electroconvulsive therapy, depression

Introduction

Electroconvulsive therapy (ECT) is an effective treatment mainly for severe forms of depression and schizophrenia that do not respond to pharmacotherapy. According to experts electroconvulsive therapy belongs to the most effective biological treatments in psychiatry and is often used in treatment of treatment-resistant depression [1]. Over years technique of performing ECT has been repeatedly modified and refined, including introduction of relaxant drugs and short-acting anaesthetics [2]. They use not only increased safety, but also tolerance of ECT. At the same time, choice of anaesthetic

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drug affects many parameters of seizures, including its duration and, indirectly, clinical effect, hemodynamic and cognitive functions [3, 4]. There are no strict guidelines regarding choice of anaesthetic for ECT, it always depends on assessment of individual risk, coexisting somatic disorders or medications [5]. Despite APA recommendations on use of methohexital [2], other drugs such as thiopental, etomidate, propofol or ketamine are widely used in ECT. Clinical experience and research findings pointed the phenomenon of increasing seizure threshold by some anaesthetics, which limits their use [5]. Based on the background of research, etomidate and ketamine, devoid of significant anticonvulsant effects compared to propofol or thiopental, may prove to be more useful for ECT [6]. It seems interesting to perceive ketamine as one of strategies to improve effectiveness of ECT [7]. Ketamine is an anaesthetic with a duration of action of 15 to 60 minutes, showing no depressive effect on respiratory centre. On the other hand, drug's cardiotoxicity, increasing blood pressure, heart rate, and cardiac output, as well as the ability to induce transient dissociative states and long time needed for patients awakening is a potential obstacle to its wider use [8, 9].

Glutamate is an excitatory neurotransmitter that plays a role in synaptic plasticity, processes of learning and memory. It acts through receptors present in four forms. Three of them are referred to as ionotropic receptors: AMPA, NMDA and kainite; the fourth one is metabotropic receptor abbreviated as mGluR. Ketamine acts on many receptors, among others as uncompetitive NMDA (N-methyl-D-aspartate) receptor antagonist with high affinity. It has less impact on sigma receptor 1, opioid receptor μ and serotonin and norepinephrine transporters. Ketamine, blocking the NMDA receptors on GABA interneurons in the prefrontal cortex, cause disinhibition of glutamate release. Released glutamate activates postsynaptic AMPA receptors mediating fast excitatory neurotransmission. AMPA stimulation starts initially ERK and AKT signal transduction cascade, at the end activating mTOR which results in protein synthesis and increased synaptic density of dendritic spines. There is an ongoing discussion concerning the main mechanism of ketamine fast antidepressant action: whether it is a blockade of NMDA receptors or follow-activation of AMPA or increased density of dendritic spines alone [10, 11]. Research confirms changes in glutamatergic system in the pathophysiology of depression and effects of antidepressants on the system [12].

Berman et al. were first that draw attention to antidepressant properties of ketamine. In a randomised study of patients with diagnosis of major depression according to DSM-IV, ketamine administered intravenously in subanaesthetic doses (0.5 mg/kg) rapidly reduced symptoms severity measured by Hamilton Depression Rating Scale (HDRS). The effect was short-termed, and results in HDRS reached baseline scores 1–2 weeks after drug injection [13]. Similar results were obtained by American authors confirming rapid resolution of depressive symptoms in patients who received ketamine. Clinical response was observed after 24 h in 71% of them comparable to 6–8 weeks of treatment with an antidepressant [14]. In a study of 10 patients, a rapid antidepressant effect of ketamine was observed, lasting on average 19 days after the

sixth infusion. Only 1 patient reported symptoms of mild depression after 3 months [15]. Similarly, beneficial effect of a single infusion of ketamine (0.5 mg/kg) was obtained in patients with bipolar depression receiving mood stabilizers. Statistically significant reduction in HDRS scale score was recorded after 24 hours of administration of ketamine. After 14 days remission was observed in 40% of patients. Authors draw attention to the correlation between a favourable response to ketamine in patients with alcohol dependence [16]. In addition, they suggest that higher concentrations of serum vitamin B_{12} levels may be associated with antidepressant effects of ketamine [16, 17]. Rybakowski et al. found a relationship between serum concentration of brain-derived neurotrophic factor (BDNF) and response to a single infusion of ketamine. BDNF concentration was significantly lower after 7 days of ketamine infusion in patients without antidepressant effect [18]. In contrast, following intravenous administration of ketamine (0.5 mg/kg) to 5 patients diagnosed with treatment-resistant depression, including ECT, in 4 of them a slight, transient clinical improvement was observed, which did not confirm earlier observations [19]. Over time attention was also drawn to the fact that the use of ketamine may be limited by side effects such as euphoria, confusion, cognitive impairment or transient dissociative states [13, 14], hence there is fear of possibly exacerbation of psychopathological symptoms in patients. Clinical observations indicate that the risk of dissociative symptoms depends on a dose. It was found by application of subanaesthetic doses (0.1–0.5 mg/kg). Incidents of psychomimetic ketamine action or stimulation were not observed when used in full anaesthetic doses in ECT (0.7–2.8 mg/kg) [8]. From the moment of observing a rapid antidepressant effect of ketamine studies on its use in ECT have been conducted with hope for increasing treatments effectiveness or accelerating their action. Minimal effect of ketamine on seizure threshold compared to other anaesthetics, enabling use in patients with an inadequate response to previously performed ECT, has been emphasised [20]. Hoyer et al. retrospectively evaluated the effect of various anaesthetics both on seizure duration and other parameters of 3,329 performed ECT. The analysis showed no differences in seizure activity using ketamine or etomidate. Administration of both drugs resulted in longer period of seizures compared to thiopental. Etomidate, in contrast to ketamine, was associated with longer seizure activity compared to propofol. Further research confirmed that use of ketamine or thiopental was associated with higher rates of postictal suppression, distinguishing these two anaesthetics from etomidate. In assessing the 'quality of treatment', defined as the total score of 5 parameters (duration, CNS inhibition, amplitude, synchronicity, autonomic arousal) the use of ketamine and etomidate was associated with obtaining 'higher quality' seizure compared to thiopental. The authors specified 31.1% of treatments in the ketamine treatment group and 33.1% in etomidate group as 'perfect' or 'near ideal'. This, according to the authors, classifies ketamine and etomidate as anaesthetics which may be preferred in ECT compared to other substances in the context of quality of treatments and thus their clinical efficacy. Simultaneously, 47.3% of ketamine seizures resulted in postictal increase in blood pressure and systolic blood pressure

over 200 mmHg as compared to lower values in case of using etomidate, thiopental or to the lowest values in case of propofol [21].

The results of synergistic antidepressant effect of ketamine with ECT are not clear. Okamoto et al. reported a rapid clinical effect in patients with severe treatment-resistant depression undergoing ECT, which were anaesthetised with ketamine. Individuals were randomly assigned to groups in which propofol (n = 20) or ketamine (n = 11) was used. Statistically significant clinical improvements were achieved by patients in ketamine group compared to propofol; differences observed after 2nd and 4th ECT, disappeared after 6th and 8th treatment. Importantly, in 2 patients of ketamine group improvement was observed despite a history indicating ineffectiveness of ECT in the past with the use of other anaesthetic [9]. In a retrospective comparison of patients who used ketamine (n = 16) or thiopental (n = 26) during ECT, Kranaster et al. have shown that patients of ketamine group required fewer treatments to achieve remission after treatment and showed a considerably lower score in HDRS. The presence of psychotic symptoms or electrodes placement had no effect on the final results. Also, the results of MMSE (Mini-Mental State Examination) both at the beginning and at the end of ECT series were slightly lower in the thiopental group, suggesting its negative impact on cognition. In the ketamine group urapidil was more often used because of elevated blood pressure. There was no difference between groups in terms of charges used or percentage of patients who used unilateral electrode placement. Postictal agitation was observed in 4 patients (15.4%) after the use of thiopental, which was not observed in ketamine group. Limitations of this study include its retrospective character, small population size and the possibility of uneven distribution of patients for the presence of psychotic symptoms or stimulating electrodes placement [4]. In contrast, Krystal et al. analysed the effects of conversion from methohexital to ketamine during ECT in 36 patients because of too short duration of seizures despite use of maximum charges allowed by FDA (Food and Drug Administration), or with shortening duration of seizures during ECT. 30 patients (83%) had a longer duration of seizures by using ketamine. In 23 patients in whom duration of seizure was less than 25 seconds with the use of methohexital, switching to ketamine resulted in extension of this parameter, and EEG analysis revealed an increase in both intraictal percentage of low-amplitude waves and postictal suppression. There is an evidence of relationship between the degree of postictal suppression and therapeutic response [22], explaining more effective ECT with the use of ketamine. Past observations concerned, however, methohexital, therefore, their referring to ketamine still remains debatable. A comprehensive orientation after ECT returned quickly, and use of ketamine was safe and well tolerated, despite trend of increasing diastolic blood pressure [20]. Ghasemi et al. attempted a comparison of antidepressant effect of ketamine with ECT in 18 patients with diagnosis of major depression according to DSM-IV. In this study one group received 3 ketamine infusions (0.5 mg/kg over 45 minutes); in the second group three ECT were performed at 48 hours each. Statistically significant reduction in severity of depression was achieved in the group receiving ketamine after

both the first and the second injection, and throughout the study period compared to ECT. Most pronounced, 42% reduction in illness severity was obtained after the first administration of ketamine, while in 44% of patients scoring scales assessing depression halved. Only in 3 patients after intravenous administration transient increase in systolic blood pressure and heart rate were observed. The authors conclude about quick, but short-term antidepressant effect of ketamine [23]. In a randomised trial involving 29 patients with diagnosis of major depression according to DSM-IV, ketamine was compared to thiopental. Cognitive functions and severity of depression were assessed by MMSE and HDRS respectively. After series of 6 ECT in both groups clinical improvement was achieved, but statistically significant reduction in severity of depression, and faster normalisation of cognitive functions were observed only before 2nd ECT with ketamine. Seizure duration was longer using ketamine, and current charges used during ECT were growing linearly in both groups, but to a greater degree when using thiopental [24].

On the other hand, there are papers which question the therapeutic superiority of ketamine in ECT. Rassmussen et al. described patients who were randomly assigned to methohexital (n = 17) or ketamine (n = 21) group. In each patient, severity of depression was assessed using the Patient Health Questionnaire-9 scale and HDRS; cognitive functions were measured by MMSE. Hemodynamic parameters and side effects after waking were also evaluated. After performed treatment statistically significant differences in scales assessing severity of depression, cognitive impairment or in the range of postoperative confusion were not observed between two groups. At any time of this study there was no advantage of ketamine. There were no differences in waking time; however, the ketamine group patients often reported subjective feeling of disorientation. The use of ketamine was associated, moreover, with a slight increase in systolic blood pressure. The use of ketamine resulted in longer duration of seizure, while differences in initiating charge dose for both anaesthetics were not observed. In summary, faster antidepressant action has not been confirmed. Perhaps, as authors suggest, ketamine increases antidepressant effect of ECT only at the beginning of series, which decays with time. At the same time they pay attention to benefit of ketamine use, which is extension of seizures duration, with a view to use in situation of its shortening as a result of other anaesthetics use [25]. The potential impact of subanaesthetic dose of ketamine (0.5 mg/kg) added to a standard thiopental anaesthesia was studied in 18 patients treated with ECT. Severity of depression was evaluated using HDRS at baseline and at 24 and 72 hours after 1st and 6th ECT. The authors did not obtain evidence for acceleration of therapeutic response in group receiving additional ketamine. There was no difference in HDRS scores in both groups after 1st and 6th ECT. There were also no evidences for rapid antidepressant effect of ketamine immediately after its administration, which stays in contradiction to previous reports. Authors did not observe extending of seizure duration by ketamine suggesting possible participation of other drugs in inducing this phenomenon [26]. A team led by Loo in a randomised, double-blind study evaluated the antidepressant effect of ketamine on ECT and the possibility of its protective ef-

fect on cognitive functions. A population of 51 patients was divided into two groups, in which they additionally received ketamine (0.5 mg/kg) or placebo with the primary anaesthetic – thiopental. There were no statistically significant differences in results of neuropsychological tests between groups suggesting a lack of protective effect of ketamine on cognitive functions during ECT. Also extended duration of seizures in ketamine group was not observed. After administration of ketamine a slightly greater improvement in depressive symptoms was shown only in first week of treatment and one week after ECT [27]. Effects of ketamine S-isomer during ECT in people diagnosed with treatment-resistant depression (n = 32) were determined. Before propofol injection subjects received a bolus of S-ketamine (0.4 mg/kg) or placebo. No statistically significant differences were obtained between patients in terms of regression of depression symptoms, rate of response to ECT or number of treatments. Similarly, no differences were found in charges applied, durations of seizures or changes in seizure threshold. Patients woke up around the same time; however, those who received S-ketamine presented a higher percentage of post treatment confusion and anxiety [28].

Ketofol is a mixture of ketamine and propofol in proportions which, according to researchers, have a beneficial effect on seizure duration compared to propofol and cause less hemodynamic side effects compared to ketamine. Yalcin et al. divided a population of 80 patients into 3 groups, respectively receiving propofol, ketamine and ketofol as an anaesthetic for ECT. Seizure duration was significantly shorter in propofol group, at the same time in all groups no significant differences were described in terms of side effects. Using ketofol was associated with greater hemodynamic security in comparison to ketamine and propofol. Recovery time was, however, superior in the ketamine group compared to propofol and ketofol [29]. In a study of Wang et al. 48 patients diagnosed with depression were divided into three groups, one of which received propofol at a dose of 1.5 mg/kg, ketamine at a dose of 0.8 mg/kg, and the third a mixture of the two anaesthetics. Changes were evaluated on HDRS scale before and a few days after the first treatment, and then it continued when the clinical situation demanded it. Faster relief of depression symptoms, higher seizure energy rate and longer duration were recorded in ketamine and ketofol groups compared to propofol. Adverse events were rare in ketofol group compared to ketamine, due to propofol silencing the excessive cardiovascular activation induced by ketamine [30].

Recapitulation

From the studies conducted so far emerge a promising prospect of using rapid antidepressant effect of ketamine, especially in combination with ECT. Reports on results of such proceedings are not conclusive. It seems that in light of published works the main benefit from the use of ketamine in ECT is lengthening of seizure duration, which would translate into increased clinical efficacy of treatments. Due to a small number of studied populations and often retrospective nature of research it is

difficult to draw far-reaching conclusions. Many key issues concerning effectiveness and sustainability of observed changes still require further exploration covering much larger group of patients.

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