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Comparison of the effect of intravenous anesthetics used for anesthesia during electroconvulsive therapy on the hemodynamic safety and the course of ECT

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Summary

Electroconvulsive therapy (ECT) is the treatment method widely used in psychiatric disorders such as depression, bipolar disorder, schizophrenia and schizoaffective disorder. The advantage of ECT is therapeutic response that occurs significantly earlier than during pharmacotherapy. Initially ECT was used without anesthesia. Then, in the 1950s procedures with general anesthesia were introduced to reduce the complications that may occur during a seizure caused by ECT, such as broken bones, teeth, tendon rupture, muscle damage. Currently, in general anesthesia for ECT several medications are used interchangeably: thiopental, propofol, etomidate and ketamine. In different resorts and different countries different anestethics are used, the choice is determined mainly by the experience of each resort and a kind of tradition. The authors provide an overview of objective data showing how various anesthetics affect the quality of ECT and the presence of any hemodynamic complications after ETC. Selection of articles included in this paper was made by searching Medline and PubMed databases using specific keywords: electroconvulsive therapy, general anesthesia, the risks and benefits of thiopental, ketamine, propofol and etomidate. The results of this review are inconclusive when it comes to the effect of intravenous anesthetics on the quality of the ECT treatment and side effects relating to respiratory and cardiovascular system. On this basis it is impossible to determine which of intravenous anesthetics is most advantageous from the point of view of the patient. To develop the optimum scheme of anesthesia for ECT, it is necessary to conduct further, methodologically correct studies.

Key words: anesthesia, electroconvulsive therapy, intravenous anesthetic

Introduction

Electroconvulsive therapy (ECT) has been a widely used method of treatment in patients with depression, bipolar disorder, schizophrenia and schizoaffective disorders since the 1930s.

ECT is currently used in North and South America, Europe, Asia, and Africa. In Australia and New Zealand, the procedure is recommended especially to the patients with bipolar and unipolar disorders; in the USA, the therapy is administered mainly (72%–92%) to the patients suffering from depression, with schizophrenia and schizoaffective disorders constituting merely 8%–24% of the total number of recommendations. In Europe, it is depression that is the disorder most often treated with ECT; only in Hungary and the Asian countries the procedure is administered especially to the patients with schizophrenia [1].

Undoubtedly, the procedure's merit lies in its significantly quicker therapeutic response than in the case of pharmacotherapy, since the improvement appears already during the first week of treatment. This is crucial for the patients with severe depressive symptoms whose condition does not improve even when other forms of pharmacological treatment have been administered, what, in turn, leads to a life-threatening situation [2].

In the acute phase of the disorder, ECT is usually administered two times per week ;10–12 procedures *in toto*. If the outcome of the treatment is favorable, the improvement of the patient's condition can be usually noticed after the sixth procedure. When the acute phase is gone, it is sometimes recommended to continue the supportive treatment; the procedures are conducted once a week and, then, once a month to prevent the relapse [3].

One of the most important parameters of ECT efficiency is the duration of the electric discharge, which should range from 25 to 75 seconds at its optimum. The duration of 15 seconds is considered too short, whereas the one of 125 seconds – too long [1].

According to the American Psychiatric Association there are no "absolute" contraindication to ECT. Specific conditions when ECT is associated with an increased risk of serious morbidity or mortality are unstable or severe cardiovascular condition, aneurysm or vascular malformation, increased intracranial pressure (which may occur with some brain tumors), recent cerebral infarction, pulmonary conditions such as severe chronic obstructive pulmonary disease, asthma or pneumonia, and patient status rated as ASA level 4 or 5 [4].

Initially, ECT was administered without anesthesia, what might result in fractured bones and teeth as well as spine injuries. Thus conducted procedure made patients apprehensive of it and Miloš Foreman's movie *One flew over cuckoo's nest*, (unfortunately) supported that fear. The scene when ECT is administered seems to be one of those images which are most commonly associated with psychiatry – and, sadly, this is not a positive image.

In the 1950s, the procedures were conducted under general anesthesia, with the administration of intravenous anesthetics and neuromuscular-blocking drugs. The aim of using succinylcholine (a depolarizing neuromuscular blocking agent) is to reduce the side-effects mentioned above: fractured bones, teeth, torn tendons, muscle injuries, which might occur during the convulsions caused by ECT. However, the administration of succinylcholine does not prevent the muscle and joint pains. Intravenous anesthetics are to minimize both the risk of unpleasant sensations, such as paralyzed muscles (caused by succinylcholine) and the level of the patient's fear of the treatment itself.

At present, ECT is conducted under general anesthesia and in accordance with the regulations of the American Psychiatric Association. Nevertheless, in some Asian countries, such as Nepal or Japan, the therapy is still conducted without anesthetization. The international regulatory considerations related to the very administration of the procedure notwithstanding, there are significant differences in conducting the therapy in various countries. These differences concern, for instance, the choice of anesthetic substances (which depends on a given center's preferences and experiences) [1, 5, 6].

An ideal anesthetic used during the ECT procedure should work instantly and for a short period of time; neither should it affect the duration and quality of electric discharges, nor compromise the organism's hemodynamic status [7]. The majority of intravenous anesthetics have dose-dependent anticonvulsant effects. They might also rise the convulsive threshold and inhibit the spread of seizures activity. These elements are, in turn, of outmost importance for ECT as it is believed that an efficient therapeutic seizure is to last at least 25 seconds. Methohexital (0.5–15 mg/kg) was the first intravenous anesthetic used during ECT for a long time as it was a safe, efficient and cheap drug. It was considered as the gold standard for anesthetic agents for ECT and remains the standard for comparison but it is no longer available. The lack of its availability has initiated the use of thiopental, propofol, etomidate and ketamine which seem to be appropriate alternatives [6, 8].

Methohexital in ECT

Methohexital, a barbiturate anesthetic, possesses dose-dependent anticonvulsant properties, and its use can interfere with effective seizure therapy in patients with high seizure thresholds. The dose range recommended by the Royal College of Psychiatrists was 0.75–0.9 mg/kg and by the American Psychiatric Association 0.75–1.0 mg/kg. A regional survey from Edinburgh in Scotland found that 52 patients referred for ECT in routine clinical practice in Edinburgh received a methohexital dose exceeding the dose range (1.5±0.3 mg/kg). An explanation for the larger methohexital dosage might be related to the concurrent chronic medications that the patients were receiving at the time of their ECT treatment, chronic consumption of alcohol and centrally active drugs (e.g., benzodiazepines) known to increase the anesthetic requirement [9].

Ding and White [9] showed that thiopental compared with methohexital shortens the EEG seizure duration, increases the frequency of sinus bradycardia and premature ventricular contractions. Anesthetic induction with etomidate, compared with methohexital, is generally associated with a longer seizure duration and may be helpful in patients with short seizure times (< 20 s) despite a maximal electrical stimulus. Early recovery after etomidate can be delayed because of post-ECT confusion and an increased incidence of emetic symptoms. The use of a minimal dose of propofol (0.75 mg/kg) was associated with a comparable seizure duration to standard doses of methohexital. The ECT seizure duration after larger dosages of propofol (1.0–1.5 mg/kg) was significantly shorter than after methohexital. With ketamine hemodynamic parameters were increased compared with those of methohexital and other intravenous drugs because of its intrinsic sympathomimetic activity. Surprisingly, the EEG

seizure duration was decreased compared with methohexital, even with small doses of ketamine.

Hooten and Rasmussen [10] analyzed 41 randomized controlled trials that compared induction agents (propofol, methohexital, midazolam, thiopental, sevoflurane, etomidate, propanidid, methohexital-remifentanil, propofol-alfentanil, propofol-remifentanil thiopental-remifentanil, thiamylal and propofol-alfentanil) with each other for ECT in adult patients (aged > 18 years) diagnosed with major depression, schizophrenia, schizoaffective disorder or bipolar disorder. Mean motor seizure duration and mean EEG seizure duration were significantly longer in the methohexital group compared with propofol.

Krystal et al. [11] carried out a retrospective analysis of data on 36 patients who were switched from methohexital to ketamine anesthesia, primarily because of short seizures (≤ 25 s) at the maximum stimulus intensity. Their results indicated that the switch to ketamine increased ECT seizure duration and that this effect was greatest when the duration at the methohexital treatment was less than 25 seconds. Significantly greater midictal amplitude accompanied the use of ketamine. These findings supported the view that ketamine might have a less potent anticonvulsant effect than methohexital. The finding of shorter post-treatment reorientation time following a switch to ketamine provided preliminary evidence that less ECT-associated retrograde amnesia might be expected with ketamine than methohexital anesthesia.

According to Yen et al. [12], ketamine anesthesia resulted in higher number of side-effects (nausea, dysphoria and dizziness that lasted from half a day to three days), higher subject dropout rates, and a longer reorientation time compare with methohexital. No significant difference in post-anesthesia recovery time was found between the ketamine and methohexital arms. Intolerability to ketamine affecting a significant proportion of subjects might be an issue that many patients and practitioners may struggle with.

Advantages and disadvantages of thiopental in ECT

Thiopental is a highly liposoluble analogue of barbituric acid. The patient should fall asleep within10–20 seconds after the administration of one dose of the drug, that is, 3–5 mg/kg. Thiopental lowers the cerebral metabolic rate for oxygen, which leads to the constriction of the cerebral vessels, lowering the cerebral blood flow and decreasing the intracranial pressure. The drug shows anticonvulsant effects but does not induce analgesia. Barbiturates depress the cardiovascular and respiratory systems (depending on the dose) what, in turn, results in the negative inotropic effect, lowering the blood pressure as well as increasing the oxygen consumption and coronary blood flow and the risk of arrhythmia caused by premature ventricular constriction. Moreover, thiopental induces a dose-dependent decrease in the respiratory rate and volume [13, 14].

In the 2011–2013 study conducted by Eser et al. [15], the patients anesthetized with propofol in Clinic I were compared with those anesthetized with thiopental in Clinic II. The results revealed that propofol caused less adverse cardiovascular and respiratory effects. In Clinic I, ECT was administered to 86 patients, whereas in Clinic II – to 103 patients. The patients anesthetized with thiopental experienced more adverse

cardiovascular (bradycardia – 16, hypertension – 7, hypotension – 1) and respiratory (apnea, acute respiratory distress syndrome – 6) effects in comparison to the patients anesthetized with propofol (bradycardia – 5, hypertension and hypotension – 0, apnea and acute respiratory distress syndrome – 0). However, the duration of the electric discharge applied to the patients anesthetized with thiopental was longer than in the group of patients anesthetized with propofol. During the first ECT procedure, the thiopental patients experienced a weaker electric current than the propofol patients. The results of the study might suggest that although thiopental is a less safe drug than propofol (the former may increase the risk of adverse effects), it allows to prolong the duration of seizures, what is of crucial importance in the efficiency of ECT [15].

Ingram et al. [16] compared thiopental and propofol administration for ECT in terms of associated clinical efficacy (authors compared response rates after 6 sessions and a tendency for higher depression levels at 1 month) and cognitive function impairment (verbal, visual, language, attention). Clinical rating scales and a battery of neuropsychological tests for the assessment of clinical efficacy of ECT and cognitive impairment were used at baseline (before intervention), after 6 sessions, 1 to 3 days after treatment end point, and at 1-month follow-up. As the result thiopental administration was associated with advantages in clinical efficacy and cognitive side effects compared with propofol administration. Although limited by small sample size, results of this study suggest that thiopental has advantages for use as an anesthetic agent with ECT compared with propofol. The study of Purtuloğlu et al. [17] supports the contrary conclusion. In his randomized trial 96 patients with major depression were administered either propofol or thiopental. None of the patients had previously received ECT. Ongoing medical treatment with antidepressants, antipsychotics, mood stabilizers or benzodiazepines was stopped one week before ECT administration. The Hamilton Depression Rating Scale was used at baseline and after 6 sessions. Aldrete and Kroulik's postanesthetic recovery score was used to assess the duration of recovery and readiness for discharge from a recovery unit. The most striking finding of this clinical trial was that propofol was associated with a greater decrease in HDRS score than thiopental. According to this study propofol may improve major depressive disorder more than thiopental in patients receiving ECT [17].

Zahavi and Dannon [6] compared retrospectively three groups of patients treated with ECT and anesthetized with thiopental (n = 39), etomidate (n = 29) and propofol (n = 23). The thiopental patients were administered a significantly weaker dose of electric current than the propofol and etomidate patients, which, in turn, did not affect in any negative manner whatsoever the length of the motor epileptic seizure. Quite the opposite – the seizure lasted statistically longer in the thiopental group. On the other hand, the length of the epileptic seizure monitored with EEG was comparable in the thiopental and etomidate patients, but considerably shorter in the propofol patients. The thiopental and propofol patients had a raised diastolic pressure, while all patients had a raised systolic pressure. The cardiac cycle was slower in the etomidate group, whereas in the other groups it did not change [6].

In a retrospective study, Eser et al. [15] compared the patients anesthetized with thiopental to those anesthetized with methohexital, etomidate and propofol. The results

showed that the length of epileptic seizure depended on the intravenous anesthetic. The longest discharge was achieved in the thiopental group. The after-seizure indicator of suppression was statistically higher in the thiopental and propofol groups. The highest clinical efficiency was achieved in the propofol and thiopental groups. There was no differences when it comes to adverse cardiovascular effects in all four groups of patients.

Rosa et al. [18] described the influence of propofol, etomidate and thiopental on the cardiovascular system in the small group of depressive patients (n = 30) treated with ECT. The patients who took part in the research had no cardiovascular medical history and did not take any antihypertensive drugs. The authors analyzed the impact of the intravenous anesthetics mentioned above on both diastolic and systolic pressure as well as on the cardiac cycle. The parameters were analyzed before the administration of the anesthetic and immediately after the end of the seizure. The researchers did not observe any statistically significant differences in the impact of the drugs on the measured parameters. Therefore, it is possible to conclude that propofol, etomidate and thiopental can be safely administered to the patients treated with ECT who have not had cardiovascular medical history [18].

In another research, Rosa et al. [19] analyzed the influence of three intravenous anesthetics: propofol, etomidate and thiopental, on the awakening time after the ECT procedure. The patients' condition was scored on the basis of Aldrete-Kroulik index. The awakening time was the shortest in the propofol group although those patients were treated with the strongest electric current during the procedure. It seems, however, that such a difference is of lesser importance as it amounts to 2 minutes only.

Hoyer et al. [20] analyzed retrospectively the influence of the intravenous anesthetics: thiopental, ketamine, etomidate and propofol, on both the length of the epileptic seizure and other parameters. The results showed no differences in the impact of ketamine and etomidate on the seizure; moreover, both drugs prolonged the seizure's length, what is in contrast to thiopental's activity. What is more, it was proven that the use of ketamine and thiopental correlated with the higher indication of the seizure suppression what differentiated them, in turn, from etomidate. While considering the "quality of therapy" understood as the evaluation of five parameters (duration, central inhibition, amplitude, synchrony, stimulation of the autonomic nervous system), it is possible to state that the use of ketamine and etomidate resulted in the seizures of "higher quality" when compared to those achieved with thiopental. 31.1% of the procedures conducted with the use of ketamine and 33.1% of those with the use of etomidate were designated as "ideal" or "almost ideal." That fact, according to the authors, could qualify ketamine and etomidate as the preferable anesthetics for ECT due to the quality of the procedure and its clinical efficiency. At the same time, 47.3% of seizures obtained with the use of ketamine resulted in the higher after-seizure blood pressure, with the diastolic pressure over 200 mmHg compared with the etomidate group (23.8% of seizures), the thiopental group (29.2% of seizures) and the propofol group (7.1% of seizures) [20].

Yoosefi et al. [21] compared the influence of thiopental and ketamine on the very course of ECT; their results seem to favor the latter. Having divided the patients into

two groups – the first anesthetized with ketamine ($n = 15$) and the other – with propofol ($n = 14$) – the authors evaluated the patients' cognitive functions on the basis of the MMSE (Mini Mental State Examination), assessed the severity of depression using the HDRS (Hamilton Depression Rating Scale) as well as rated the amperage used for the procedure and analyzed the duration of the epileptic seizure, blood pressure, cardiac cycle before the first and the second procedure, and, subsequently, a couple of days and a month after the sixth procedure. In both groups of patients, the severity of depression was significantly reduced after the sixth procedure. However, before the second ECT procedure conducted in the ketamine group, there was observed a considerable statistical difference in HDRS score. What is more, when rated on the basis of the MMSE, the cognitive functions of the patients anesthetized with ketamine revealed a significant improvement, although it must be stressed that the MMSE test is not an optimal device for evaluating the cognitive functions under such circumstances. The epileptic seizure during the procedure were also significantly longer in the patients anesthetized with ketamine; the dose of an electric current was being increased in both groups proportionally to the duration of the entire therapy. A considerable increase of blood pressure was observed in the ketamine group, whereas the differences between both groups when it comes to tachycardia were not statistically significant [21].

Wisniewski et al. [22] did not find a significant difference in the brain natriuretic peptide (BNP) levels between the group with thiopental anesthesia alone and the group with alternating anesthesia of thiopental and ketamine. BNP is a physiological marker of cardiac muscle overload and normal BNP level is a credible indicator of lack of acute or chronic cardiac failure. This study showed that using ketamine as an anesthetic for ECT seemed to be as safe for the circulatory system as the use of thiopental. But this research is limited by the small group of its participants. It should be also stressed that only patients without any cardiovascular contraindications were qualified to ketamine anesthesia. Therefore it cannot be ruled out that the most beneficial effect in the ketamine group might have been influenced by a better somatic condition of patient, which could also be important when it comes to the initial state of depression [22].

The study conducted by Eser et al. on a relatively small number of patients shows that the use of thiopental during ECT correlates with an increased number of adverse cardiovascular and respiratory effects [15]. That result is not, however, fully in accordance with the characteristics of those drugs since it is propofol that affects more the respiratory and cardiovascular systems [13, 14]. The use of thiopental allows to prolog the duration of the epileptic seizure during ECT, what is of crucial importance in assessing the efficiency of this type of therapy [6]. Moreover, thiopental is a safe drug for the patients with no previous cardiovascular medical history [16]. The awakening time after the procedure, when the patient was anesthetized with thiopental, was longer than with propofol. However, such information seems to be not that important as the difference amounts to 2 minutes only [17]. The use of thiopental correlates with a higher quality of ECT (the evaluation based on the duration of the procedure, central inhibition, amplitude, synchrony, stimulation of the autonomic nervous system) when compared to the use of propofol, but lower – if compared to etomidate or ketamine [18]. The study of Ingram et al. [16] suggested that using thiopental resulted in greater

clinical efficacy in ECT therapy than using propofol. On the contrary, Purtuloğlu et al. [17] indicated that propofol is more suitable than thiopental in terms of ECT treatment effectiveness

Advantages and disadvantages of propofol in ECT

Propofol is a phenol derivative, slightly soluble in water. If administered intravenously in 2–2.5 mg/kg doses, it leads to the loss of consciousness within 25–40 seconds which lasts about 8 minutes. The drug produces dose-dependent depression of the cerebral cortex. It also has anticonvulsant effects. Due to its dose-dependent decrease in vascular resistance, propofol also induces a decrease in systemic peripheral resistance and lowers central venous pressure. The reduction in both preload and cardiac contractibility leads to a decrease in stroke volume and hypotension. When compared to thiopental, propofol significantly reduces vascular resistance as well as lowers blood pressure and stroke volume. The respiratory depression caused by propofol is stronger than the one induced by thiopental [13, 14].

In a group of 34 patients with schizophrenia, Gazdag et al. [23] studied the influence of propofol and etomidate on the duration of the epileptic seizure during the ECT procedure monitored with EEG and EMG, as well as on the cardiovascular system (mean arterial blood pressure, heart rate). When compared to etomidate, the use of propofol correlated with a shortened, to 13.4 seconds and 12.7 seconds, duration of electric discharge monitored with EEG and EMG, respectively. On the basis of the study it is possible to state that etomidate should be administered when there is no possibility of obtaining a 20-second duration of electric discharge with propofol at full dose. The raised mean arterial blood pressure in the propofol group was statistically, yet significantly, lower than in the etomidate group. Therefore, propofol seems to be a preferable drug for the patients with the risk of adverse cardiovascular effects [23]. On the other hand, Rosa et al. [18] did not notice any differences in the influence of propofol, etomidate and thiopental on diastolic or systolic pressure and heart rate during ECT. Such discrepancies in the results of the studies might result from the fact that the patients from the research conducted by Gazdag et al. were simultaneously receiving psychotropic medication, whereas those from the study conducted by Rosa et al. were solely subjected to ECT.

The results of the research conducted by Erdil et al. [24] showed that it was propofol and not etomidate that did not prolong the QT section during the ECT procedure. Hence, propofol did not increase the risk of arrhythmia. In the propofol group there was observed a statistically significant lower increase of mean arterial pressure and heart rate immediately after the procedure.

Jarineshin et al. [25] compared the effects of thiopental and propofol on seizure duration and hemodynamic parameters during ECT. The patients with a history of hypertension, diabetes mellitus, renal failure, neuromuscular and heart disease were excluded. The mean duration of seizure in the thiopental group was significantly longer (40.32±3.81) than in the propofol group (32.02±11.36). There was no statistically significant difference between the mean energy level applied in the two groups. The mean

systolic and diastolic blood pressure at all times after seizure and mean heart rate at 3 and 5 minutes after seizure were significantly lower in propofol than in thiopental groups. According to this study, propofol provides a more stable hemodynamic state for the ECT procedures and its use is highly preferred over thiopental in patients with cardiovascular diseases. This study also had limitations. The included patients did not have any concurrent disease and if this was done in patients with underlying medical disease, the result may have been different [25].

Stadland et al. [26] proved that the patients anesthetized with propofol who could not experience an epileptic seizure longer than 30 seconds, though administered with the strongest electric current, might also be anesthetized with other intravenous anesthetic (for instance, etomidate) in order to prolong the duration of the seizure to 18–43 seconds.

Tufek et al. [7] analyzed 1,342 ECT procedures administered to 179 patients who were anesthetized with propofol, etomidate or ketamine. The rate of the procedures considered inefficient due to a duration shorter than 20 seconds was statistically considerably higher in the propofol group and amounted to 16.8% when compared to the etomidate and ketamine groups (4% and 3.7%, respectively). The longest epileptic seizure monitored with EEG was in the ketamine group. The study confirmed that propofol is a fast-acting drug with a short awakening time which does not affect the patients' cognitive functions.

Another study conducted by Swaim et al. [27] proved that the administration of a considerably higher electric current to the propofol patients significantly shortened the length of epileptic seizures when compared to the patients anesthetized with thiopental. Therefore, it seems reasonable to claim that the risk of inefficient (too short) seizures is considerably higher in the propofol rather than in the thiopental groups.

In the study by Kumar et al. [3], the first group of 14 patients was anesthetized for the ECT procedure with propofol at a dose of 1.5 mg/kg and the second group of 14 patients with thiopental at a dose of 3 mg/kg. Diagnosed with depression or bipolar disorder, the patients anesthetized with propofol needed a larger number of procedures than the thiopental patients to reach a comparable therapeutic effect; that fact, however, did not affect the length of hospitalization, which was similar in both groups. A stronger electric current administered to the propofol patients resulted in a statistically longer electric discharge monitored with EEG when compared to the thiopental patients; the awakening time was also significantly longer in the thiopental group. Although in both groups of patients raised systolic pressure and tachycardia were observed immediately after the procedure, the percentage increase of those parameters was statistically significantly higher in the thiopental group. Moreover, when evaluated on the basis of the Beck Depression Inventory (BDI) and the MMSE, the results of the patients from both groups did not reveal significant differences. After the course of ECT treatment, in the group of patients anesthetized with propofol there was a statistically significant decrease in the BDI rating. As assessed on the basis of the MMSE, the recovery of cognitive functions after the ECT procedure was comparable in both groups of patients [3].

However, Butterfield et al. [28] presented a different outcome of their research as they claimed that the recovery of cognitive functions in the early stage of awakening

after the ECT procedure was significantly shorter when the patients were anesthetized with propofol rather than with thiopental.

The results published by Bauer et al. [29] indicate that propofol, when compared to thiopental, considerably shortens the duration of the procedure, which does not affect the efficiency of treating depression. The propofol patients, who were administered with a considerably higher electric current during the procedure, obtained a significantly worse screening result of cognitive functions rated on the basis of the MMSE; that fact, however, might be caused by uneven age distribution in the examined groups of patients.

The current state of knowledge on the influence of intravenous anesthetics in ECT is full of contradictions. Some literature data may suggest that due to its anticonvulsant activity, propofol considerably shortens the length of the monitored epileptic seizures when compared with other anesthetics – hence, a number of seizures can be considered inefficient [7]. On the other hand, the academic literature also informs that the use of propofol does not affect the efficiency of ECT in treating depression [30, 31]. Nevertheless, one study revealed that after the course of ECT treatment, the group of patients anesthetized with propofol obtained a statistically significant decrease in the BDI rating when compared to the thiopental patients [3]. Propofol provides a more stable hemodynamic state for the ECT procedures and its use is highly preferred over thiopental in patients with cardiovascular diseases [25]. The awakening time after the procedure is shorter in comparison to other intravenous anesthetics; hence, propofol seems not to affect cognitive functions after ECT [7, 28]. The use of propofol resulted in the lowest quality of ECT (the evaluation based on the duration of the procedure, central inhibition, amplitude, synchrony, stimulation of the autonomic nervous system) when compared to etomidate, ketamine and thiopental [20]. Propofol seems to be a safe anesthetic used during the ECT procedure as its administration results in the smallest increase of heart rate as well as a small percentage of the after-seizure increased blood pressure when compared to the patients anesthetized with ketamine, thiopental and etomidate [20].

Advantages and disadvantages of etomidate in ECT

Etomidate is imidazole carboxylate which induces general anesthesia after 30–40 seconds. Its administration often results in epileptic-like seizures monitored with EEG. Cerebral blood flow, intracranial pressure, intraocular pressure and cerebral metabolic rate for oxygen are lowered. The drug does not induce the cardiovascular depression to such an extent as thiopental does; hence, etomidate is favored for the patients who have the cardiovascular medical history. It does lower the respiratory rate and volume, although the intensity of respiratory depression is less severe than when barbiturates are used. Etomidate blocks 11ß-hydroxylase and cholesterol metabolism, thus also blocking corticosteroids and mineralocorticoids syntheses. The intravenous administration of a single dose of etomidate suppresses the synthesis of steroids for 6 hours. When compared with other anesthetics, etomidate correlates with the longest period of the epileptic seizure as it has the weakest activity and, at the same time, anticonvulsive effect which is independent of the dosage [13, 14]

Some sources claim that etomidate used during the ECT procedure allows to obtain the longest electric discharge when compared to thiopental and propofol. That result may be of practical importance in patients who are exposed to shorter electric discharge (< 20 seconds) despite the administration of the strongest electric current. On the other hand, the use of etomidate may increase a number of adverse cardiovascular effects as well as prolong the awakening time and increase the frequency of vomiting when compared to propofol [7, 26].

In the study conducted by Tufek et al [7], etomidate was used during 278 ECT procedures performed on 42 patients; only 3.9% of the procedures were considered inefficient due to the duration of the electric discharge, which was not long enough. When the ECT procedures were regarded as inefficient, the patients, initially anesthetized with propofol, were administered etomidate and, as a result, the electric discharge was prolonged to > 40 seconds. Other retrospective research proves that patients anesthetized with etomidate experience longer seizures during the ECT procedure and a smaller number of electric discharges shorter than 20 seconds despite administering a weaker electric current, compared to propofol.

Many studies have confirmed that etomidate suppresses the synthesis of steroids [32]. Lebowitz et al. [33] conducted the ACTH stimulation test on two groups of patients treated with ECT. In the first group, anesthetized with etomidate, the test was repeated every 2–3 days, whereas in the second one – anesthetized with methohexital – after the first and the last procedure. Then, every subsequent procedure was preceded by a serum cortisol level test. In both groups no suppression of synthesis of steroids was observed. Therefore, it might be surmised that the majority of patients anesthetized with etomidate may have a lower cortisol level, which returns to normal before the next ECT procedure.

During ECT treatment, it seems reasonable to replace propofol or thiopental with etomidate when the seizures last shorter than 20 seconds, in order to prolong seizures [7, 26, 34]. Nevertheless, some research reveals that the use of thiopental correlates with longer seizures when compared to etomidate and propofol [15]. While evaluating the "quality of ECT" (the evaluation based on the duration of the procedure, central inhibition, amplitude, synchrony, stimulation of the autonomic nervous system), Hoyer et al. [20] stated that the use of ketamine and etomidate correlated with a "higher quality" of procedures when compared with the use of thiopental. A study conducted by Erdil et al. [24] shows that etomidate prolongs the QT section during ECT, thus increasing the risk of arrhythmia.

Advantages and disadvantages of ketamine in ECT

Ketamine is a phencyclidine derivative. Following intravenous administration, the drug starts to act after one minute. Ketamine produces dissociative anesthesia, that is, a type of cataleptic state when a patient seems to be detached from the environment and one's self, however, this is not coterminous with regular sleeping. Moreover, the state is accompanied by analgesia and amnesia. Having been anesthetized with ketamine, the patient's awakening time is longer when compared to other anesthetics

and the very process may induce hallucination, diplopia or temporary loss of vision. After the administration of the drug, cerebral blood flow, cerebral metabolic rate for oxygen, intraocular pressure and intracranial pressure are raised. Ketamine increases the risk of arrhythmia as well as raises both mean arterial pressure and the level of catecholamine due to a general increased activity of CNS. The drug does not induce depression of the respiratory system [13, 14].

By raising intracranial pressure and mean arterial pressure, ketamine is not favored in ECT [7, 26]. The drug may also produce the adverse effects such as euphoria, confusion, impairment of cognitive functions or temporary dissociative states, although the latter depend, as the research shows, on the dosage. The dissociative states are confirmed when ketamine is administered in subanesthetic doses (0.1–0.5 mg/kg). No psychotomimetic incidents or agitation have been observed when the drug was administered during ECT in full doses (0.7–2.8 mg/kg) [35–37].

Berman et al. [35] highlighted the antidepressant effect of ketamine. In a randomized study, the patients diagnosed with very severe depression (according to DSM-IV) were receiving intravenously subanesthetic doses of the drug (0.5 mg/kg), which alleviated the severity of depressive symptoms as assessed on the basis of the HDRS (Hamilton Depression Rating Scale). The therapeutic effect was short-lived and the HDRS rating returned to its initial results 1–2 weeks after the injection. Similar results were obtained by Zarate et al. [36], which confirmed a rapid reverse of depressive symptoms in the patients treated with ketamine. A clinical reaction was observed after 24 hours in 71% of patients, what was comparable to 6–8 weeks of antidepressant treatment. That result was not, however, confirmed by the study conducted at the Institute of Psychiatry and Neurology in the patients diagnosed with drug-resistant depression who were also resistant to the ECT procedures [38].

Also Rybakowski et al. [39], in his study which included 53 patients (13 men, 40 women), showed a rapid antidepressant effect of a single ketamine infusion in a considerable proportion of those patients with bipolar depression receiving one or more mood-stabilizing medications (authors divided them into first and second generation). Pre-infusion depression intensity on the HDRS was 23.4±4.6 points and the assumed criterion for response was a reduction of ≥ 50% in the HDRS score after 7 days. The antidepressant effect of ketamine was observed in 27 subjects (51%), more frequently in males (77%) than females (43%).

In another study, Rybakowski at al. [40] noted that the addition of ketamine might be associated with better antidepressant efficacy of ECT, compared with only thiopental anesthesia. In three groups of patients with drug-resistant depression measured by the HDRS, fifteen patients – group 1 received only thiopental anesthesia, 15 patients – group 2 had their second and third ECT session with ketamine, and 15 patients – group 3 had ketamine for the second, fourth, sixth, eight and tenth session. As the result this study showed that after the last ECT session, the intensity of depression was significantly lower in group 3, compared with group 1. However, replacing thiopental with ketamine for the second and third session did not produce a better clinical effect. Cognitive assessments after ECT showed a more marked worsening in verbal memory in patients with added ketamine anesthesia. The main limitation of this study was the

problem with randomization. For the patients with any contraindication for ketamine, all ECT sessions were performed with thiopental anesthesia and only patients with no contraindications to ketamine could be randomized in group 2 and 3. It is possible that patients anesthetized with ketamine were in better somatic condition, which could influence the outcome of treatment [40].

In the study of Loo et al. [41] 51 depressed patients were randomized to receive either ketamine (0.5 mg/kg) or saline in addition to thiopental during anesthesia for ECT. Neuropsychological outcomes (measured before ECT, after six sessions, and after the end of ECT treatment) did not differ between groups. The addition of ketamine did not decrease cognitive impairment in patients, but was safe and slightly improved efficacy in the first week of treatment and at one-week follow up. The ECT-ketamine group had a slightly greater improvement in depressive symptoms over the first week of treatment and at one-week follow up, though there was no overall difference in efficacy at the end of the ECT treatment.

Järventausta et al. [42] randomized 32 patients with a severe recurrent depressive disorder with treatment resistance. For induction of anesthesia the ketamine group first received ketamine (0.4 mg/kg) as a bolus and then propofol, and the second group first received saline and then propofol. A statistically significant and clinically relevant reduction in the depressive symptom scores was found in both study groups. There was no difference in the magnitude or speed of decrease in depressive symptoms between the study groups, nor was there any difference in the numbers of ECT sessions, seizure thresholds, seizure durations, and the electrical doses. The patients from both groups recovered from anesthesia equally, but the degree of posttreatment disorientation and restlessness was more marked in the ketamine group.

Also the study of Fernie at al. [43] demonstrated that ketamine as an anesthetic for ECT does not enhance the efficacy of ECT compared to propofol. Using the ketamine did not result in fewer ECT sessions, improvements in depression severity ratings and less memory impairment than the standard anesthetic.

Anderson et al. [44] recruited for their study severely depressed patients having unipolar or bipolar disorder with depressive episode defined as moderate or severe by DSM-IV criteria. Patients were randomly assigned to ketamine bolus or saline adjunctive to propofol or thiopental during their ECT treatment (40 patients in the ketamine group vs. 39 in the saline group). ECT procedures were administered twice weekly. Ketamine, compared with saline, had no significant impact on the neuropsychological outcomes and efficacy outcomes. This study do not support the use of adjunctive low-dose ketamine in routine ECT treatment.

An antidepressant effect of ketamine resulted in an interest in and research on its use during ECT in hope of increasing the procedures' efficiency and activity. Okamoto et al. [45] described a quick clinical effect on patients diagnosed with severe drug-resistant depression who were anesthetized with ketamine rather than with propofol. The patients were assigned randomly to the propofol (n = 20) and the ketamine (n = 11) groups. A statistically significantly quicker clinical improvement was noted in the ketamine group; the positive effect was evaluated multiple times on the basis of the HDRS before the first procedure and after the second, fourth, sixth and eight

one. It must be stressed that the condition of two patients from the ketamine group did improve despite the fact that their medical history indicated ECT's inefficiency when other anesthetics were used.

Ghasemi et al. [46] compared antidepressant effect of ketamine with efficiency of ECT administered to 18 patients diagnosed with severe depression according to DSM-IV. The first group was administered three intravenous injections of ketamine (0.5 mg/kg in 45 minutes); the second – three ECT procedures at intervals of 48 hours. When compared to the ECT group, a statistically significant and quicker improvement was observed in the ketamine group immediately after the first and second intravenous administration as well as in the overall study period. Moreover, on the basis of the study in 17 patients diagnosed with severe drug-resistant depression who did not respond positively to previous ECT treatment and in 23 patients who were not treated with ECT at all, Ibrahim et al. [47] proved that ketamine correlated with alleviating depressive symptoms within 230 minutes after the intravenous administration of the drug at the dose of 0.5 mg/kg.

In the study conducted by Wang et al., 48 patients diagnosed with depression were divided into three groups [48]. The first group was anesthetized with propofol (1.5 mg/kg), the second – with ketamine (0.8 mg/kg) and the third – with the mixture of both drugs. The changes in the HDRS score were assessed before the first procedure and then one, two, three and seven days after ECT. A statistically significant decrease in the HDRS score was found in the patients anesthetized with ketamine and the mixture of ketamine and propofol (ketofol). A higher rate of seizure and its longer duration was noted in the ketamine and ketofol groups, compared to the propofol group. The adverse effects were less frequent in the ketofol group when compared to the ketamine group. The reason might be that propofol blocked excessive stimulation of the cardiovascular system, which was induced by ketamine.

The study of Salehi et al. [49] indicated that ketamine and thiopental had a significant effect on the reduction of depression scores in patients with drug-resistant depression. Adverse effects such as a headache, nausea, pain at the injection site, short – and long-term disturbances of consciousness, were more frequent in ketamine group. Ketamine was more effective in improvement of depression score and increasing systolic and diastolic blood pressure. Anesthesia induced by ketamine during ECT therapy increased blood pressure and seizure duration. According to this study due to higher impact of ketamine versus thiopental on decreasing of the HDRS score and recovery of depressive patients, ketamine is more appropriate for anesthesia in ECT in depressive patients.

Abdallah et al. [50] analyzed the influence of a subanesthetic dose of ketamine (0.5 mg/kg) added to a standard dose of thiopental and administered to 18 patients treated with ECT. The severity of depression was assessed on the basis of the HDRS at the beginning and within 24 and 72 hours after the first and sixth procedure. No significantly lower scores were observed in both groups after the first ECT procedure. What is more, neither did the authors observe a therapeutic improvement in the group with additional ketamine. A significantly lower score assessed on the basis of the HDRS was observed in both groups after the sixth procedure. In contrast to the previous research, the authors did not observe quick antidepressant effect of ketamine.

Ketamine minimally affects the seizure threshold, what makes the drug favorable for the patients who have not responded to the previous ECT treatment. In the study conducted by Krystal et. al. [11], in the course of ECT treatment, 36 patients were anesthetized with ketamine instead of methohexital. In 24 out of 36 patients, the change of the anesthetic was caused by too short seizures, lasting less than 25 seconds, monitored with EEG despite using the strongest electric current approved by the FDA (Food and Drug Administration); in 10 out of 36 patients the change was caused by shortening of duration of seizures, close to 25 seconds; and two patients had hypotension and pruritus when anesthetized with methohexital. After the change of the drug 30 patients (83%) experienced longer seizures and 23 out of 24 patients who had been initially anesthetized with methohexital experienced seizures that lasted longer than 25 seconds when anesthetized with ketamine.

The literature provides the information about antidepressant effect of ketamine [36, 39, 46, 49]. This feature could be of a great value during the ECT procedures, thus improving the efficiency of treating depression. However, not all authors confirm antidepressant effect of ketamine [35, 38, 50]. While evaluating the "quality of ECT" (the evaluation based on the duration of the procedure, central inhibition, amplitude, synchrony, stimulation of the autonomic nervous system), Hoyer et al. [20] indicated that the use of ketamine correlated with a "higher quality" of procedures when compared with the use of thiopental and propofol. At the same time, the highest percentage of the increased mean arterial pressure, with systolic pressure over 200 mmHg, was observed in the ketamine group when compared to a lower percentage in the etomidate, thiopental and propofol groups [20]. The study conducted by Tufek et al. [7] revealed that when the patients were anesthetized with propofol, etomidate or ketamine, the longest epileptic seizure monitored with EEG was noted in the ketamine group. Nevertheless, since ketamine can produce dissociative anesthesia, it may not be favored during ECT due to the possibility of exacerbating psychiatric symptoms [20].

Recapitulation

Today, the choice of drugs used for anesthesia during ECT depends mostly on country and the center where procedures are performed. The criterion for selection of a particular anesthetic is tradition rather than evidence-based medicine [1, 5, 6]. The results of the latest research on the benefits and risks for the patient resulting from the use of intravenous anesthetics such as thiopental, etomidate, ketamine, and propofol, are not clear. Table 1 shows the summary information on the individual drugs, presents their mechanism of action, impact on hemodynamic parameters and impact on quality of ECT sessions. All barbiturates increase the seizure threshold and shorten the duration of the seizure with the least effect being observed for methohexital, which is why in many countries it is the most commonly used anesthetic in ECT, so-called gold standard. Currently available data does not allow to determine which of the anesthetic would be best for the patient and it is not possible to make a clear first choice recommendation as a replacement for methohexital.

For the moment it is up to the anesthetist which drug will be used and it is also related to the drug availability. The four above-mentioned intravenous anesthetics would seem to be acceptable alternatives for methohexital although each drug has its disadvantages. Some disadvantages can be minimized by using the lowest effective dose required for safe and adequate anesthesia. Each center needs to gain experience with more than one anesthetic agent (e.g. in case of unavailability of one of the agents).

Further investigation is needed to develop the optimal procedure. Their goal should be the emergence of such a measure which would combine hemodynamic safety with minimal adverse effect on quality of the ECT treatment.

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Table 1. **Comparison of anesthetics**

Drug	Mechanism of action	Impact on hemodynamic parameters	Impact on the quality of ECT
Thiopental	thiobarbiturate, enhances the activity of GABA-A receptors in the brain and produces hypnotic and anticonvulsant effect	nervous system – CBF ↓, ICP ↓, IOP ↓, CMRO2 ↓; cardiovascular system – BP ↓, CVP ↓, negative inotropic agent, CO ↓, HR ↓; risk of arrhythmia ↑; respiratory system – RF ↓, TV ↓	Better quality of ECT when compared to the propofol group, but lower – when compared to the etomidate and ketamine groups. Shorter duration of seizures when compared to the ketamine and etomidate groups, but longer – when compared to the propofol group; increased central inhibition compared to the etomidate group.
Ketamine	phencyclidine and cyclohexane derivative, inhibits NMDA (analgesic effect) and muscarinic acetylcholine receptors, influences opioid μ, κ, δ receptors, stimulates sympathetic nervous system	nervous system – ICP ↑, CBF ↑, CMRO2 ↑, IOP ↑; cardiovascular system – HR ↑, CO↑, BP ↑, CVP ↑; respiratory system – dilates bronchi, does not involve hypoventilation	Better quality of ECT when compared to the thiopental and propofol groups, and comparable to the etomidate group. Longer duration of seizures when compared to the thiopental group, and comparable to the etomidate group; increased central inhibition when compared to etomidate; the highest percentage of increased BP, with systolic pressure over 200 mmHg when compared to the thiopental, propofol and etomidate groups.
Propofol	Alkylphenol derivative, enhances the activity of GABA-A and glycine receptors, inhibits nicotinic neuronal receptors, produces anticonvulsant effect	nervous system – ICP ↓, CPP ↓, CMRO2 ↓; cardiovascular system – BP ↓, CVP ↓, CO ↓, does not affect HR; respiratory system – TV ↓, RF ↑	The lowest quality of ECT when compared to the ketamine, etomidate and thiopental groups. Shortens duration of seizures monitored with EEG and EMG; induces the smallest increase of heart rate when compared to the thiopental, ketamine and etomidate groups; fast-acting drug with a short awakening time; does not affect the patients' cognitive functions.
Etomidate	Imidazole carboxylate, enhances the activity of GABA-A receptors	nervous system – IOP ↓, CBF ↓, ICP ↓, CMRO2 ↓; cardiovascular system – MAP ↓, HR ↓; respiratory system – TV ↓, RF ↓	Better quality of ECT when compared to the thiopental and propofol groups, and comparable to the ketamine group; longer duration of seizures when compared to the thiopental group, and comparable to the ketamine group.*

CO – cardiac output; CBF – cerebral blood flow; ICP – intracranial pressure; IOP – intraocular pressure; CMRO2 – cerebral metabolic rate for oxygen; HR – heart rate; CVP – central venous pressure; RF –respiratory frequency; TV – tidal volume; CPP – cerebral perfusion pressure; MAP – mean arterial pressure. *Note: Induces adrenal insufficiency if used in long infusions; induces epileptic-like seizures; prolongs the QT section; the weakest and independent of the dose anticonvulsant effect.