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Investigation of Electroconvulsive Therapy Parameters in Propofol and Ketamine–Propofol Combination Anesthesia

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ABSTRACT

Objective: It is aimed to highlight the concept of electrical stimulus [electroconvulsive therapy (ECT) dose], an aspect that has not received sufficient attention in previous research on ECT.

Methods: This study is a retrospective investigation aiming to examine the medical records of patients who received ECT. Patients were assigned to 2 groups. The first group received a dose of 1mg/kg propofol for ECT anesthesia (n = 25), while the second group receives a combination of 0.5 mg/kg propofol and 0.5 mg/kg ketamine (n = 36).The electrical charge required to induce an effective seizure and the parameters determining the electrical charge, such as pulse width, frequency, stimulus duration, and current, were recorded at each session and compared.

Results: In propofol group the initial value of frequency was 29.03 ± 7.35 Hz and the last value (frequence at eighth session) was 83.06 ± 24.45 Hz. The difference in frequency was found to be significantly increased in propofol group ($F = 151.95$; $\eta p^2 = 0.83$; $P < .0001$). In propofol + ketamine group the initial value of frequency was 24.09 ± 7.42 Hz and the last value (frequence at eighth session) was 91.74 ± 22.39 Hz. The difference in frequency was found to be significantly increased in propofol group ($F = 237.05$; $\eta p^2 = 0.95$; $P < .0001$). The duration of session was significantly decreased in propofol group ($F = 10.29$; $\eta p^2 = 0.28$; $P < .0001$). The duration of the seizure in first session was 57.17 ± 19.09 seconds and the duration of seizure in eighth session was 50.78 ± 14.21 seconds in propofol + ketamine group. The duration of the session was significantly decreased in propofol + ketamine group.

Conclusion: It was observed that the ECT dose remained similar between the 2 groups. Further research is warranted to delve into the cognitive effects of the propofol + ketamine combination in ECT procedures.

Keywords: Cognitive, ECT, depression, dose, frequency

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INTRODUCTION

Electroconvulsive therapy (ECT) is a medical procedure that entails the application of electric current to stimulate brain tissue, ultimately leading to the induction of generalized seizures.[1] Electroconvulsive therapy is predominantly employed in the management of psychiatric conditions, including depressive disorders, mania, schizophrenia, schizoaffective disorder, and specific other psychotic disorders.

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Moreover, it finds utility in addressing conditions like catatonia, Parkinson's disease, neuroleptic malignant syndrome, and treatment-resistant epilepsy. In general, ECT is recognized as a highly effective and safe therapeutic approach; nevertheless, one of the most frequently observed side effects of ECT is cognitive impairment.[2]

Electroconvulsive therapy procedures are performed using anesthesia and muscle relaxation. The anesthetic agents used during ECT anesthesia should have a short duration of action, not affect seizure activity or duration, facilitate rapid recovery, and have minimal impact on hemodynamics. Anesthetics such as thiopental (2-3 mg/kg), methohexital (0.5-1.0 mg/kg), ketamine (0.5-1 mg/kg), etomidate (0.15-0.3 mg/kg), and propofol (0.75-1.5 mg/kg) can be used to provide anesthesia.[3] Propofol, owing to its anticonvulsant properties, raises the seizure threshold, requiring a higher electrical charge to induce a successful seizure. This elevation in electrical charge has been linked to the most frequently encountered side effect of ECT, which is cognitive impairments.[4] Ketamine exhibits a lower anticonvulsant effect when compared to other anesthetics. Moreover, research has been conducted on the antidepressant qualities of ketamine, and it has been noted that there is an improvement in depressive symptoms within 24 hours following the intravenous infusion of subanesthetic doses of ketamine (0.5 mg/kg) in depressed patients. The psychomimetic and cardiotoxic effects associated with ketamine have prompted the exploration of its use in subanesthetic doses, often in combination with propofol.[5] The combination of ketamine and propofol in ECT anesthesia is a more common practice. In the literature, some studies using propofol + ketamine in ECT anesthesia have shown an earlier onset of antidepressant effect and better cognitive performance.[6-8] However, these studies did not take into account the electrical charge administered during ECT.

The aim of this study is to compare the antidepressant effect and the total electrical stimulus (ECT) required for achieving effective seizures between propofol and ketamine–propofol combination in anesthesia for ECT. Additionally, we aim to emphasize the concept of ECT dose, which has not been adequately addressed in previous studies on ECT.

MATERIAL AND METHODS

This study is a retrospective analysis conducted to review the medical records of patients who underwent ECT and were diagnosed with major depressive disorder as per the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition.[9] The study period covered patients treated between January, 2019, and January, 2020, at our clinic. Upon admission to the psychiatric ward, individuals scheduled for ECT received both verbal and written information sessions explaining the procedure, and their informed consent was obtained through a consent form specifically designed for ECT. Patients diagnosed with "major depressive disorder" and selected for ECT at our clinic were categorized into 2 groups. The first group received a dose of 1mg/kg propofol for ECT anesthesia (n = 25), while the second group receives a combination of 0.5 mg/kg propofol and 0.5 mg/kg ketamine (n = 36). In both groups, a muscle relaxant, rocuronium at a dose of 0.3 mg/kg, was administered. The assessment of antidepressant response was carried out using the Hamilton Depression Scale, which was administered before the commencement of treatment and subsequently at the second, fourth, sixth, and eighth sessions. Additionally, the electrical charge necessary to induce an effective seizure and the parameters influencing the electrical charge, including pulse width, frequency, stimulus duration, and current, were documented during each session. The study conducted at Tekirdağ Namık Kemal University, Faculty of Medicine obtained approval from the Medical Ethics Committee for Non-Interventional Studies. The ethics approval number assigned to the study was 46048792-050.01 .04-E-11411, and the approval was issued on February 2, 2020.

Electroconvulsive Therapy Procedure

The ECT sessions took place twice a week and employed bitemporal electrode placement. The SpECTrum 5000Q device manufactured by Mecta (Tualatin, Ore, USA), was used, with brief pulse settings, which was described in previous studies.[10] All ECT procedures were performed by a highly trained team consisting of psychiatrists and anesthesiologists.

Anesthesia Application

The anesthesia team in charge of each session made decisions regarding the specific types and quantities of anesthetic drugs and muscle relaxants to be used, primarily considering factors such as drug availability and the team's own preferences.

Measurement Tools

Electroconvulsive Therapy Consent Form: A form prepared by the Department of Psychiatry at Tekirdağ Namık Kemal University, Faculty of Medicine, providing general information about ECT, risks, side effects, and precautions to be taken, is used to inform the patient or legal representative about ECT and obtain their consent.

Hamilton Depression Scale: This scale measures the level and severity of depression in patients. It is administered by an interviewer and was developed by Hamilton in 1960. The Turkish validity and reliability study was conducted by Akdemir et al[11] in 1996. The scale consists of 17 items, with a maximum score of 53. Scores between 0 and 7 indicate "no depression," between 8 and 15 indicate "mild depression," between 16 and 28 indicate "moderate depression," and scores above 29 indicate "severe depression."

Statistical Methods

The obtained data will be analyzed using the Statistical Package for the Social Sciences Statistics software program for Windows 17 (SPSS Inc.; Chicago, IL, USA). The normality of the data obtained through counts will be determined using the Shapiro–Wilk normality test to assess whether they are parametric or not. The differences in numerical parametric values between 2 groups will be determined using the Student's *t*-test. Nonparametric numerical variables will be analyzed using the Mann–Whitney *U*-test for binary groups. The chi-square test will be applied for categorical variables, and if necessary, the Fisher exact test will be used. A repeated measures analysis of variance is used to determine whether or not there is a statistically significant difference between the means of the variables of ECT and the scores of HDRS (Hamilton Depression Rating Scale) during the eighth session. The significance level for all variables will be set at $P < .05$. Count data will be presented as mean ± standard deviation, while categorical variables will be presented as percentages.

RESULTS

The mean age of the propofol group was 41.36 ± 10.62 years, and it was 45.60 ± 12.30 years in the propofol + ketamine group. There were 6 males (24%) and 19 females (76%) in propofol + ketamine group, whereas there were 20 males (55.6%) and 16 females (54.4%) inpropofol group. The male ratio was found to be significantly higher in propofol group ($P = .016$). The 10 participants were single (27.8%),

and 26 participants were married (72.2%) in propofol group. In propofol + ketamine group, 2 participants were single (8%) and 23 participants (92%) were married. The groups were found to be similar in terms of marriage status ($P = .60$). The 22 of patients (61.1%) in were smokers and 14 of them (39.9%) were nonsmokers in propofol group, whereas 17 of patients (68%) in were smokers and 8 of them (32%) were nonsmokers in propofol + ketamine group ($P = .78$). The family history of a psychiatric disorder existed in 12 patients (33.3%) in propofol group and in 10 patients (40%) in propofol + ketamine group ($P = .61$). Thirty-two patients have been receiving antidepressant treatment (88.9%) in propofol group, and 19 patients have been receiving antidepressant treatment (76%) in propofol + ketamine group during admission ($P = .29$).

In propofol group, the initial value of frequency was 29.03 ± 7.35 Hz, and the last value was (frequence at eighth session) 83.06 ± 24.45 Hz. The difference in frequency was found to be significantly increased in propofol group ($F = 151.95$; $\eta p^2 = 0.83$; $P < .0001$) (Figure 1). In propofol + ketamine group the initial value of frequency was 24.09 ± 7.42 Hz, and the last value was (frequence at eighth session) 91.74 ± 22.39 Hz**.** The difference in frequency was found to be significantly increased in propofol group ($F = 237.05$; $\eta p^2 = 0.95$; $P < 0.0001$) (Figure 2). The duration of the seizure in first session was 54.19 ± 9.36 seconds, and the duration of seizure in eighth session was 44.85 ± 14.61 seconds in propofol group. The duration of session was significantly decreased in propofol group ($F = 10.29$; $\eta p^2 = 0.28$; $P < .0001$) (Figure 3). The duration of the seizure in first session was 57.17 ± 19.09 seconds, and the duration of seizure in eighthsession was 50.78 ± 14.21 seconds

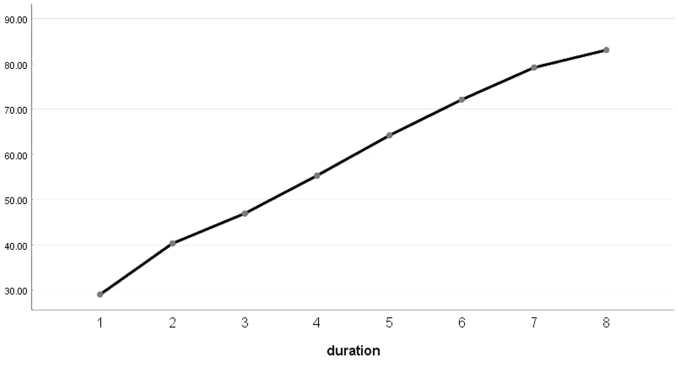

Figure 1. The change in frequency in propofol group between first and eighth sessions of electroconvulsive therapy.

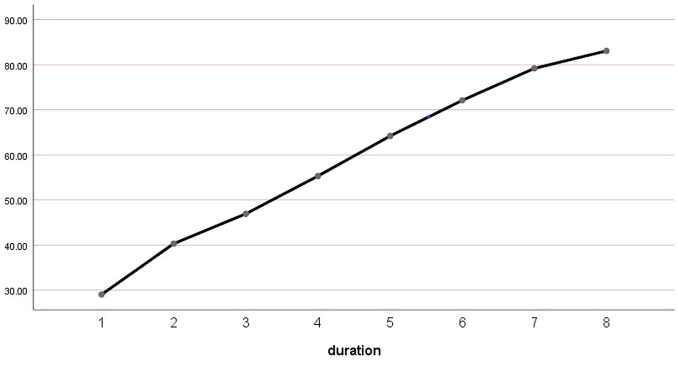

Figure 2. The change in frequency in propofol and ketamine group between first and eighth sessions of electroconvulsive therapy.

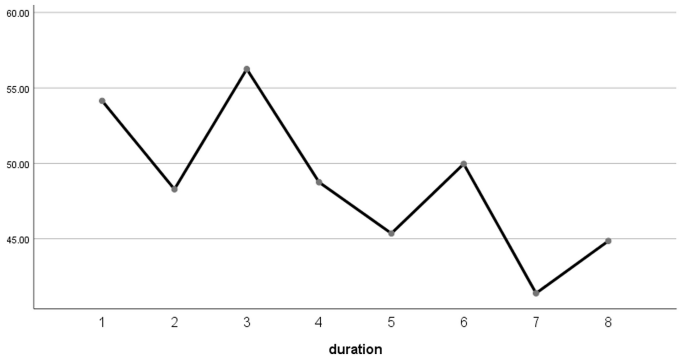

Figure 3. The change in duration of seizure in propofol group between first and eighth sessions of electroconvulsive therapy.

in propofol + ketamine group. The duration of session was significantly decreased in propofol + ketamine group ($F = 3.17$; $\eta p^2 = 0.12$; $P = .004$) (Figure 4). The initial ECT dose was 107.93 ± 30.07 mC at first session, and it was 355.70 ± 161.09 mC at eighth session in propofol group. The ECT dose significantly increased in propofol group ($F = 90.74$; $\eta p^2 = 0.75$; $P < .0001$) (Figure 5). The initial ECT dose was 86.36 ± 35.12 mC at first session, and it was 363.19 ± 139 mC at eighth session in propofol + ketamine group. The ECT dose significantly increased in propofol group ($F = 269.27$; $\eta p^2 = 0.92$; $P < .0001$) (Figure 6) (Table 1).

The scores of HDRS were significantly decreased in both groups ($F = 18.99$; $\eta p^2 = 0.52$; $P < .0001$ and $F = 17.97$; $\eta p^2 = 0.53$; $P < .0001$

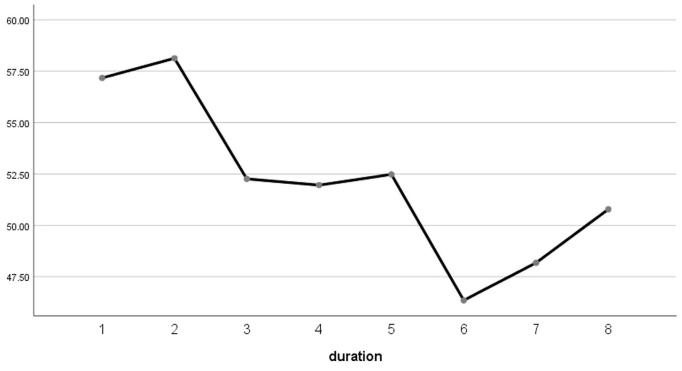

Figure 4. The change in duration of seizure in propofol and ketamine group between first and eighth sessions of electroconvulsive therapy.

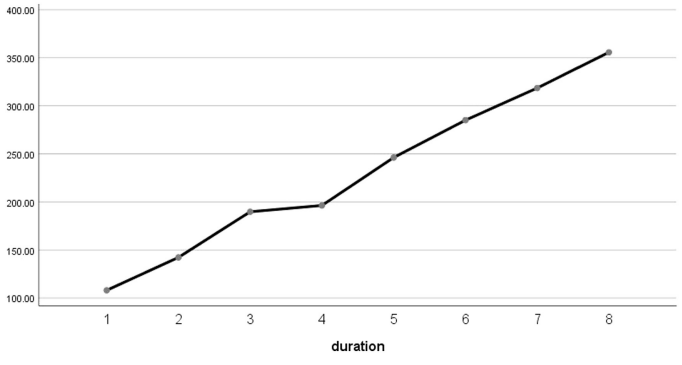

Figure 5. The change in electroconvulsive therapy (ECT) dose in propofol group between first and eighth sessions of ECT.

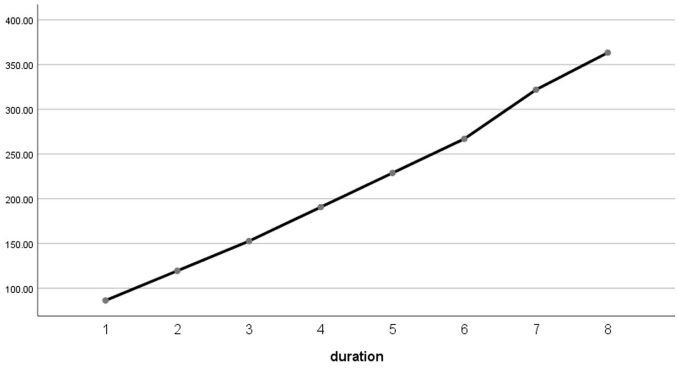

Figure 6. The change in electroconvulsive therapy (ECT) dose in propofol and ketamine group between first and eighth sessions of ECT.

Table 1. The Electroconvulsive Therapy Parameters in Each Session

Approach	Session	Frequency (Hz)	Duration (Seconds)	Load (mC)
Propofol (n = 25)	First	29.03 ± 7.35	54.14 ± 9.36	107.93 ± 30.27
	Second	40.32 ± 17.22	48.28 ± 10.55	142.17 ± 45.64
	Third	46.93 ± 6.76	56.25 ± 14.12	189.70 ± 72.78
	Fourth	55.32 ± 8.30	48.75 ± 13.87	196.25 ± 83.66
	Fifth	64.19 ± 21.72	45.35 ± 4.31	246.14 ± 83.31
	Sixth	72.09 ± 21.82	49.96 ± 12.42	285.05 ±101.68
	Seventh	79.19 ± 24.49	41.39 ± 11.26	318.48 ± 125.71
	Eighth	83.06 ± 24.44	44.85 ± 14.61	355.70 ± 161.25
Propofol + ketamine (n = 36)	First	24.78 ± 7.45	41.39 ± 11.26	86.36 ± 35.99
	Second	31.30 ± 9.79	44.85 ± 14.61	119.47 ± 47.20
	Third	41.30 ± 12.26	57.17 ± 19.09	152.73 ± 56.70
	Fourth	50.43 ± 14.05	58.13 ± 26.05	190.71 ± 57.90
	Fifth	60.00 ± 15.66	52.26 ± 13.18	228.90 ± 60.20
	Sixth	70.00 ± 17.96	51.95 ± 8.41	266.95 ± 69.04
	Seventh	84.34 ± 22.62	52.47 ± 15.11	321.95 ± 87.23
	Eighth	91.73 ± 22.39	46.34 ± 15.79	363.39 ± 106.78

mC: millicoulomb

in propofol and propofol + ketamine groups respectively). The decrease of HDRS scores was considered to be similar between the groups.

The eighth session values of frequency and duration of seizure were found to be significantly higher in propofol + ketamine group compared with propofol group ($P < .05$). The eighth session values of ECT dose and HDRS scores were similar between the groups ($P = .07$).

DISCUSSION

In the current study, we conducted a comparison between the frequencies, seizure durations, ECT doses, and HDRS scores from the initial session to the eighth session in both the propofol and propofol + ketamine groups. Significant alterations in these ECT parameters were observed in both groups.

To ensure the effectiveness and safety of ECT, it is essential to employ an ideal anesthetic induction agent with specific characteristics. Ideally, this agent should have minimal anticonvulsant properties and should not induce any hemodynamic effects. These criteria are of paramount importance in enhancing the overall outcome of ECT procedures.[12] However, it is important to note that a perfect drug meeting these exact specifications has not yet been established. Nonetheless, there are variations among the available induction agents in terms of their specific effects, providing some options for clinicians to consider when selecting the most appropriate agent for anesthetic induction during ECT.[10] One strategy for optimizing the induction anesthesia in ECT involves the synergistic combination of 2 agents with complementary properties. The objective is to develop a balanced approach that maximizes the desired effects while minimizing the adverse ones. Through the deliberate selection of agents with nonadditive anticonvulsive and hemodynamic effects, the overall anesthesia can be customized to enhance the therapeutic advantages of ECT while mitigating potential risks.[13]

In the context of ECT, propofol stands out as a promising candidate due to its remarkable anticonvulsant properties. However, it falls short in terms of its hemodynamic effects, which are generally hypodynamic in nature. Nonetheless, propofol offers an advantage of a low to negligible incidence of bronchoconstriction, making it a valuable choice for patients undergoing ECT.[14] By strategically combining agents with synergistic anesthetic properties, such as propofol with another suitable agent, it is possible to fine-tune the anesthesia induction process for ECT.[15]

Ketamine is known for its rapid and robust antidepressant effects, particularly in individuals with treatment-resistant depression. The mechanism of ketamine's antidepressant action is complex and not fully understood, but it is believed to involve several factors including *N*-methyl-D-aspartic acid receptor antagonism, synaptic plasticity, anti-inflammatory effects, and glutamate–γ-aminobutyric acid balance.[15,17] The combination of ketamine and propofol in ECT anesthesia is a more common practice. In the literature, some studies using propofol + ketamine in ECT anesthesia have shown an earlier onset of the antidepressant effect and better cognitive performance.[7-9] However, these studies did not take into account the electrical charge administered during ECT.

In recent years, there has been substantial interest in the role of ketamine as an anesthetic agent in ECT for the treatment of major depressive disorder (MDD).[18] The use of a combination of ketamine and propofol, commonly referred to as "ketofol" anesthesia, has emerged as a subject of significant interest in the context of ECT for the treatment of MDD. Studies have explored the effects of ketofol anesthesia on hemodynamic stability, particularly in critically ill patients. The results suggest that this combined anesthesia approach can enhance hemodynamic stability, leading to a more favorable cardiovascular profile when compared to other anesthetic agents. This is especially significant in the context of ECT, as maintaining stable hemodynamics is vital for ensuring patient safety and reducing potential complications during the procedure. Alongside its positive influence on hemodynamic stability, ketofol anesthesia has also shown benefits in terms of the quality of seizures.[19] Notably, despite the enhanced seizure quality achieved with ketofol, the duration of the seizures was similar to that observed with propofol alone. These findings suggest that the combination of ketamine and propofol, as ketofol anesthesia, offers potential benefits for patients undergoing ECT.[20] In present research, we have investigated the parameters of ECT including the frequencies, the duration of seizures, and ECT dose. In both groups, there were significant changes in all parameters. Additionally, the value of frequency was considered to have

changed much more in the propofol + ketamine group compared to the propofol group, and the eighth session value was found to be significantly higher in the propofol + ketamine group. Regarding the duration of seizure, we found that duration of seizure decreased significantly in both groups; however the decrease in propofol group was considered as higher compared with propofol + ketamine group, and the duration of seizure was significantly higher in propofol + ketamine group. The ECT dose, which was assumed to be related to cognitive side effects, was found to be similar between the groups. The decrease in HDRS in both the groups were similar with each other.

The present study has several limitations. First, the retrospective design can be considered as a limitation. Second, we could not use cognitive parameters with objective scales, and we solely investigated the ECT parameters and HDRS; this issue is considered to be another limitation.

CONCLUSIONS

Present study shows the favorable outcomes of propofol + ketamine combination compared with propofol use during ECT procedure. The ECT dose, which should be considered as an indicator for cognitive side effects, was found to be similar between the groups. Further studies are needed to investigate the cognitive effects of propofol + ketamine combination in ECT procedure.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Tekirdağ Namık Kemal University (Approval no: 46048792-050.01.04-E-11411, Date: February 2, 2020).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Resources – E.B.; Materials – E.B.C., A.G.; Data Collection and/or Processing – E.B., E.B.C.; Analysis and/or Interpretation – E.B., İ.Y.; Literature Search – A.G., E.B.; Writing Manuscript – E.B.; Critical Review – E.B., M.B.

Declaration of Interests: The authors have no conflict of interest to declare.

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REFERENCES

1. Fink M. M. Meduna and the origins of convulsive therapy. *Am J Psychiatry*. 1984;141(9):1034-1041. [CrossRef]
2. Margoob MA, Ali Z, Andrade C. Efficacy of ECT in chronic, severe, antidepressant- and CBT-refractory PTSD: an open, prospective study. *Brain Stimul*. 2010;3(1):28-35. [CrossRef]
3. Joung KW, Park DH, Jeong CY, Yang HS. Anesthetic care for electroconvulsive therapy. *Anesth Pain Med (Seoul)*. 2022;17(2):145-156. [CrossRef]
4. Hooten WM, Rasmussen KG, Jr. Effects of general anesthetic agents in adults receiving electroconvulsive therapy: a systematic review. *J ECT*. 2008;24(3):208-223. [CrossRef]
5. Krystal AD, Weiner RD, Dean MD, et al. Comparison of seizure duration, ictal EEG, and cognitive effects of ketamine and methohexital anesthesia with ECT. *J Neuropsychiatry Clin Neurosci*. 2003;15(1):27-34. [CrossRef]
6. Smischney NJ, Beach ML, Loftus RW, Dodds TM, Koff MD. Ketamine/propofol admixture (ketofol) is associated with improved hemodynamics as an induction agent: a randomized, controlled trial. *J Trauma Acute Care Surg*. 2012;73(1):94-101. [CrossRef]
7. Erdil F, Ozgul U, Şanli M, Kayhan G, Çolak C, Durmuş M. The effects of remifentanil on hemodynamic response attenuation after electroconvulsive therapy under sevoflurane anesthesia. *J ECT*. 2017;33(4):264-267. [CrossRef]
8. Kranaster L, Kammerer-Ciernioch J, Hoyer C, Sartorius A. Clinically favourable effects of ketamine as an anaesthetic for electroconvulsive therapy: a retrospective study. *Eur Arch Psychiatry Clin Neurosci*. 2011;261(8):575-582. [CrossRef]
9. Association AP. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed; 2013.
10. Gurel SC, Ozden HC, Karahan S, Ayhan Y. The superiority of ketofol and etomidate against propofol or thiopental anesthesia for ECT. *Asian J Psychiatr*. 2022;72:103090. [CrossRef]
11. Akdemir, A., Türkçapar, M. H., Örsel, S. D., Demirergi, N., Dag, I., & Özbay, M. H. (2001). Reliability and validity of the Turkish version of the Hamilton Depression Rating Scale. *Comprehensive psychiatry*, 42(2), 161-165.
12. Kadiyala PK, Kadiyala LD. Anaesthesia for electroconvulsive therapy: an overview with an update on its role in potentiating electroconvulsive therapy. *Indian J Anaesth*. 2017;61(5):373-380. [CrossRef]
13. Hoyer C, Kranaster L, Janke C, Sartorius A. Impact of the anesthetic agents ketamine, etomidate, thiopental, and propofol on seizure parameters and seizure quality in electroconvulsive therapy: a retrospective study. *Eur Arch Psychiatry Clin Neurosci*. 2014;264(3):255-261. [CrossRef]
14. Patel AS, Gorst-Unsworth C, Venn RM, Kelley K, Jacob Y. Anesthesia and electroconvulsive therapy: a retrospective study comparing etomidate and propofol. *J ECT*. 2006;22(3):179-183. [CrossRef]
15. Martin BA, Cooper RM, Parikh SV. Propofol anesthesia, seizure duration, and ECT: a case report and literature review. *J ECT*. 1998;14(2):99-108. [CrossRef]
16. Beserra FR, Menezes BS, Mograbi DC. Therapeutic Protocols Using Ketamine and Esketamine for Depressive Disorders: A Systematic Review. *J Psychoact Drugs*. 2023:1-17. [CrossRef]
17. Medeiros GC, Matheson M, Demo I, et al. Brain-based correlates of antidepressant response to ketamine: a comprehensive systematic review of neuroimaging studies. *Lancet Psychiatry*. 2023. [CrossRef]
18. Nagi T, Jagtiani A, Somvanshi S, et al. Ketamine augmentation of electroconvulsive therapy: A scoping review of dose-dependent effects in major depressive disorder. *Cureus*. 2023;15(6):e40087. [CrossRef]
19. Mukhtar F, Regenold W, Lisanby SH. Recent advances in electroconvulsive therapy in clinical practice and research. *FAC Rev*. 2023;12:13. [CrossRef]
20. Kritzer MD, Peterchev AV, Camprodon JA. Electroconvulsive therapy: mechanisms of action, clinical considerations, and future directions. *Harv Rev Psychiatry*. 2023;31(3):101-113. [CrossRef]