International Journal of Medical Anesthesiology

E-ISSN: 2664-3774
P-ISSN: 2664-3766
www.anesthesiologypaper.com
IJMA 2024; 7(4): 169-174
Received: 04-09-2024
Accepted: 10-10-2024

Min A Kwon
Department of Anesthesiology and Pain Medicine, Dankook University College of Medicine, Cheonan, Republic of Korea

Jaegyeok Song
Department of Anesthesiology and Pain Medicine, Dankook University College of Medicine, Cheonan, Republic of Korea

Sungmi Ji
Department of Anesthesiology and Pain Medicine, Dankook University College of Medicine, Cheonan, Republic of Korea

Yeongseok Yun
Department of Anesthesiology and Pain Medicine, Dankook University College of Medicine, Cheonan, Republic of Korea

Wonkyu Lee
Department of Anesthesiology and Pain Medicine, Dankook University College of Medicine, Cheonan, Republic of Korea

Corresponding Author:
Min A Kwon
Department of Anesthesiology and Pain Medicine, Dankook University College of Medicine, Cheonan, Republic of Korea

Comparison of remimazolam and etomidate as induction agents for electroconvulsive treatment

Min A Kwon, Jaegyeok Song, Sungmi Ji, Yeongseok Yun and Wonkyu Lee

DOI: https://doi.org/10.33545/26643766.2024.v7.i4c.527

Abstract
Background: Electroconvulsive therapy (ECT) is used to treat severe psychiatric disorders through seizure induction via electrical currents, typically under general anesthesia. Although etomidate is known to extend the seizure duration and maintain hemodynamic stability, concerns regarding its effects on the adrenocortical axis limit its use. Remimazolam, a novel ultra-short-acting benzodiazepine, offers rapid onset and recovery with a favorable safety profile. Therefore, we compared remimazolam with etomidate as induction agents for ECT, focusing on their impact on seizure activity and recovery time.
Methods: This prospective, randomized, crossover study included 30 patients aged 18–65 years scheduled for ECT with an American Society of Anesthesiologists Physical Status I and II. The primary outcomes were recovery time of self-respiration and eye opening, which were compared between the remimazolam and etomidate groups. We also recorded mean arterial pressure and heart rate at several time points and assessed the energy delivered during the shock, seizure duration, duration of recovery-room stays, and complications.
Results: There was no significant difference in the energy required to induce seizures between the etomidate- and remimazolam-treated groups. However, the motor seizure duration was significantly longer in the etomidate group than in the remimazolam group. There were no significant differences in the blood pressure, heart rate, or self-respiration recovery times between the two groups.
Conclusions: Remimazolam can effectively replace etomidate as an ECT-induction agent with comparable hemodynamic stability, recovery parameters, and seizure shock thresholds. It is particularly suitable for patients at high risk of adrenal insufficiency.

Keywords: Electroconvulsive therapy, remimazolam, etomidate, ECT-induction agent, seizure activity, recovery time

Introduction
Electroconvulsive therapy (ECT) is a psychiatric treatment involving the induction of seizures through the application of electrical currents to the brain. ECT is primarily used to treat several psychiatric disorders, such as depression, bipolar disorder, schizophrenia, and schizoaffective disorder, particularly when other treatments have proven ineffective [1]. ECT is typically administered under general anesthesia in a hospital setting, and muscle relaxants are given to prevent injuries during the induced seizure [2]. Treatment usually involves multiple sessions, typically two to three times a week, with the total number of sessions varying based on the patient's condition and response to treatment [3].
Many studies have been conducted to identify better induction agents for anesthesia in ECT. An ideal anesthetic for ECT should act rapidly and have a short duration of action. It should not interfere with the duration or quality of the induced seizures or disrupt the body's hemodynamic stability. The most used medications for anesthesia-induction in ECT include methotrexate, thiopental, etomidate, and propofol [4].
Etomidate is an intravenous (IV) induction agent known for its ability to extend seizure duration while maintaining hemodynamic stability. Despite its various advantages, etomidate has not become a popular induction agent because of concerns regarding its prolonged effects on the adrenocortical axis than initially anticipated [5].
Remimazolam is a novel IV anesthetic agent belonging to the benzodiazepine class and is characterized by its ultra-short-acting properties. It combines the benefits of rapid onset and quick recovery, making it particularly useful in procedural sedation, general anesthesia, and,

of other commonly used agents. It is associated with a lower risk of hypotension and respiratory depression than that of propofol, making it a safer option for patients with cardiovascular and respiratory concerns [7]. In addition, the effects of remimazolam can be quickly reversed with flumazenil, which is advantageous over other anesthetics that do not have specific reversal agents [8].

However, there is a lack of research on the use of remimazolam as an ECT-induction agent. Therefore, based on the rapid pharmacological profile and hemodynamic safety of remimazolam, we compared it with etomidate to evaluate its potential as an induction agent for ECT. We hypothesized that patients would wake up more quickly when using remimazolam. Furthermore, as benzodiazepines have anticonvulsant effects, midazolam is not used as an induction agent for ECT [9]. Therefore, we investigated whether remimazolam might similarly interfere with the seizure activity required for ECT. Finally, since quick recovery is beneficial for patients undergoing ECT, we also evaluated the recovery time between the two agents.

Materials and Methods

Study Design

The study protocol was approved by the Institutional Review Board of Dankook University Hospital (DKUH 2023-02-005-002). All participants provided written informed consent prior to enrollment. The study was registered at ClinicalTrials.gov with the registration number NCT06664138.

Patients who underwent ECT under general anesthesia between April 2023 and January 2024 were included. The exclusion criteria were as follows: (1) American Society of Anesthesiologists Physical Status ≥3; (2) age <18 or >70 years; and (3) patients with cognitive impairments, such as dementia or delirium. The sample consisted of 30 patients aged 18–70 years who were scheduled to undergo ECT for major depression, schizophrenia, and schizoaffective disorder. We calculated the sample size using G*Power to compare the recovery times between the two groups. Based on the effect size of 0.7 obtained from a previous pilot study and a significance level of 0.05, we derived a total sample size of 28. We also considered a follow-up loss of approximately 10%; thus, we designed the study to include a total of 30 participants.

The patients were divided into two groups of 15 each and randomly assigned to either group E or group R using a computer-generated random number table. To minimize variability in recovery speed and response to medication between individuals, we devised a crossover study design in which etomidate and remimazolam were administered alternately, with each drug administered once. Patients in group E received etomidate as the induction agent for the first ECT session, followed by remimazolam for the second ECT session a few days later. Conversely, patients in group R received remimazolam as the induction agent for the first ECT session and etomidate for the second ECT session a few days later. The patients and raters were blinded to the administered anesthetic drugs. Blinding was implemented using opaque sealed envelopes that were sequentially numbered.

ECT Procedure

ECT was conducted following the international standards approved by our institution, using the SpECTrum 5000 Q device (MECTA Corporation, Lake Oswego, OR, USA).

No premedication was administered, and all patients were required to maintain nil per so for at least 8 h before the procedure. During each ECT session, all patients underwent non-invasive blood pressure measurement, electrocardiography, and peripheral oxygen saturation (SpO_2) monitoring and received preoxygenation through an O_2 facial mask before anesthesia.

For neuromuscular blockade, succinylcholine (0.8–1.2 mg/kg IV) was used. The anesthetic dosages were etomidate at 0.15–0.20 mg/kg IV and remimazolam at 0.12–0.15 mg/kg IV. After the patient was admitted and all monitoring was completed, preoxygenation was performed until SpO2 reached 100%, followed by the administration of the induction agent, either etomidate or remimazolam. Immediately afterward, all patients were given 100 mcg of remifentanil. After confirming a lack of response from the patient when called, a cuff was placed on one arm and inflated until the radial artery pulse was no longer detectable. After isolating one arm, succinylcholine was administered, and sufficient time was allowed for fasciculation to resolve before proceeding. After adequate time for the muscle relaxant to take effect, electrical currents were delivered to the brain through electrodes placed on the scalp. The intensity of the current was determined according to an established psychiatric protocol, and in the absence of a seizure, was increased by 10 J in three successive attempts. If a seizure lasting longer than 30 s was induced, the treatment was considered successful. The duration of the seizure and corresponding shock intensity were recorded for each patient.

Following the seizure, mask ventilation was continued until spontaneous respiration returned. The time from the end of the seizure until the patient's spontaneous tidal volume reached ≥200 mL was measured and defined as the self-respiration recovery time. Additionally, the time from the end of the seizure until the patient opened their eyes spontaneously, either in response to a gentle tap or verbal stimulation, was measured and defined as the eye-opening recovery time.

Apart from the induction agent, there were no differences between the two groups in terms of procedural techniques, anesthetic management during surgery, or cardiovascular support.

Primary Outcomes

The primary outcomes were self-respiration and eye-opening recovery time. For each patient, outcomes were compiled and compared between remimazolam and etomidate. For secondary outcomes, we also recorded mean arterial pressure (MAP) and heart rate before induction (T_0), immediately after induction (T_1), immediately after shock (T_2), and at the time of awakening (T_3). Regarding the seizure profile, we measured and recorded the energy delivered during the shock and the seizure duration separately. Finally, we assessed the duration of stay in the recovery room and monitored for any adverse effects related to changes in consciousness, such as delirium or confusion.

Statistical Analysis

Quantitative variables are expressed as means and standard deviations, while qualitative variables are presented as absolute frequencies and percentages. Statistical comparisons between the groups were conducted using the

paired t-test for continuous variables and the chi-square test for categorical variables. Statistical calculations were performed using IBM SPSS Statistics for Windows, version 17 (IBM Corp, Armonk, NY, USA). A p-value <0.05 was considered statistically significant, and $p<0.001$ was deemed highly significant.

Results

The research was conducted over a period of 10 months, from April 2023 to January 2024. A total of 33 patients were evaluated for eligibility; 30 fulfilled the inclusion criteria and were included in the study. All 30 patients were administered both induction agents (Etomidate and propofol) during either the first or second ECT session, and there were no dropouts. There were no failures in inducing seizures in either group. Furthermore, there were no significant differences in patient age, sex, body weight, or psychiatric diagnosis between groups E and R (Table 1). The overall mean age of the patients was 39.4±16.7 years. They were predominantly female (66%) and had a mean body weight of 66.1±13.4 kg.

There was no significant difference in the energy required to induce seizures between the etomidate- and remimazolam-treated groups (p=0.288) (Table 2). Motor seizure duration was significantly longer in the etomidate group (60.3±37.8 s) than in the remimazolam group (47.4±19.7 s) ($p<0.05$).

Heart rate and blood pressure were recorded at baseline (T_0), after induction (T_1), immediately after shock (T_2), and in the awake state (T_3). The heart rate and blood pressure of the patients were categorized based on the use of etomidate and remimazolam, and the mean values were calculated and represented in a graph (Figures 1 and 2). Both drugs showed a decreasing trend in heart rate and blood pressure compared with the baseline after induction, followed by an increase after shock, and a subsequent decrease upon awakening. There were no significant differences in the blood pressure or heart rate between the two groups at T_0, T_1, T_2, or T_3.

The self-respiration recovery time was 279.2±92.4 s with etomidate and 259.9±105.9 s with remimazolam, showing no significant difference between the two (p=0.441) (Table 3). The eye-opening recovery time was 392.1±167.6 s with etomidate and 343.8±115.3 s with remimazolam (p=0.166). There were no significant differences in the recovery-room stay duration, and no adverse effects, such as delirium or confusion, were reported.

Discussion

ECT is a treatment option for individuals with severe depression and other psychiatric disorders who do not respond to conventional medications [1, 2]. Typically administered under general anesthesia, the selection of the best anesthetic agent has been a topic of debate because of the differing pharmacodynamics of commonly used IV drugs. Although many studies have compared various drugs suitable for ECT induction, to our knowledge, none have examined remimazolam and etomidate using a crossover design.

Post-anesthetic recovery after ECT is a critical concern that has practical implications for psychiatrists directly involved in ECT and those who prescribe it. A more comfortable treatment experience enhances patient compliance and satisfaction. Therefore, in this study, we focused on recovery after ECT and conducted a comparative analysis of the seizure profiles and hemodynamic outcomes. The study utilized a crossover design in which 30 patients were randomly assigned to receive both drugs during successive ECT sessions. Outcomes were evaluated after combining sessions in which remimazolam or etomidate was used as an anesthetic agent. The current study design effectively minimized selection bias, ensuring that the demographic distribution was comparable across both groups.

There was no significant difference in the energy delivered during the shock to induce seizures between etomidate and remimazolam. According to our institution's psychiatric protocol, the energy used to induce seizures was empirically set at 25 J for the first ECT session and increased by 10 J in each subsequent session. If a seizure was not induced or lasted <30 s, we increased the energy by 10 J and attempted two to three times to induce the seizure again. In other words, when remimazolam is used for ECT induction, appropriate seizures can be induced at the same shock energy levels as etomidate. However, the seizure duration was significantly longer with etomidate than with remimazolam.

These findings are consistent with those of previous studies, indicating that benzodiazepines can shorten the duration of seizures [9]. Furthermore, numerous studies have shown that etomidate significantly increases seizure duration compared with other induction agents used in ECT [10]. Although seizure duration with remimazolam is shorter than that with etomidate, clinical guidelines suggest that a seizure duration ≥25 s is adequate to generate a good response to ECT [11]. Considering that the average seizure duration with remimazolam in this study was 47.4 s, it can be concluded that remimazolam was effective in inducing sufficient ECT responses. In patients with a seizure duration <20 s, the use of etomidate may be more effective.

During ECT, the patient's physiology undergoes significant changes. Between electrical stimulation and the onset of the seizure, conditions such as hypotension, bradycardia, and asystole may arise because of the dominance of the parasympathetic nervous system. Conversely, tachycardia and hypertension occur during seizures because of rebound sympathetic activity [12, 13]. We measured patients' MAP and heart rate at baseline, after induction, immediately after shock, and upon awakening. When induced with etomidate and remimazolam, both groups showed similar changes in vital signs. After induction, MAP and heart rate decreased by approximately 10% compared with baseline. Immediately after the shock, MAP increased by approximately 40%, whereas heart rate increased by approximately 80%. Hypertension and tachycardia returned to near-normal levels within a few minutes, although they remained slightly elevated compared with baseline.

Hemodynamic changes were similar between the two agents; however, there was no statistically significant difference in the values. Etomidate may be particularly beneficial for patients at a high risk of cardiac complications during and after ECT as these patients rely heavily on their sympathetic tone to sustain hemodynamic stability. Additionally, etomidate may be particularly beneficial for patients with catatonia, a potentially life-threatening condition characterized by dehydration and hypotension, as it is often required as a first-line treatment owing to its minimal impact on hemodynamics. Considering that our findings indicated no significant changes in hemodynamics between etomidate and remimazolam, we can conclude that remimazolam preserves hemodynamic stability during both

seizure and non-seizure time points, making it a favorable choice for an anesthetic agent.

We set the primary outcomes as the time to return to self-respiration and the time to eye-opening in response to verbal commands. Considering the rapid onset and recovery time associated with remimazolam, we hypothesized that it would result in a shorter recovery time than etomidate and conducted our study accordingly. However, although the average self-respiration and eye-opening recovery times were both lower with remimazolam than with etomidate, the differences were not statistically significant. We also monitored the post-anesthesia care unit (PACU)-stay time and assessed adverse effects, such as postoperative delirium and confusion. Since no negative changes in vital signs, such as unstable hemodynamics or decreased SpO_2, were observed, along with the absence of mental disturbances, such as agitation, neither group showed any difference in PACU-stay time according to the established recovery room protocol. No adverse effects were reported. An important point is that a higher shock energy is often associated with a greater frequency of postictal confusion. Given that there were no significant differences in the shock energy administered between the two groups, it is reasonable to assume that there were no meaningful differences in the recovery parameters.

Etomidate has long been considered a first-line treatment for ECT in many studies. This is because of its advantages, including rapid onset, stable hemodynamics, and ability to prolong seizure duration, which contribute to its high therapeutic efficacy. In contrast, benzodiazepines have largely been avoided because their anticonvulsant effects may elevate the seizure threshold, thereby diminishing the therapeutic efficacy of ECT [9]. However, the recently introduced ultra-short-acting benzodiazepine, remimazolam, has been approved for use as an induction agent in brief procedures and general anesthesia. Nevertheless, there is a lack of research on its use as an ECT-induction agent, which motivated this study. This study revealed that remimazolam offers many of the advantages of etomidate. Both agents share benefits, such as rapid onset and stable hemodynamics, with no significant differences in the threshold energy for inducing seizures or recovery parameters. While there was a meaningful difference in seizure duration, with etomidate resulting in longer durations than those of remimazolam, remimazolam maintained the required duration of >25 s for effective treatment. Therefore, we conclude that remimazolam can be used as a first-line treatment for ECT. In addition, the risk of adrenal insufficiency associated with prolonged etomidate use and the availability of flumazenil as a reversal agent for remimazolam make it a suitable alternative to etomidate.

This study had several limitations. First, seizure duration was measured using the isolated forearm technique, which tends to underestimate the duration compared to measurements obtained through electroencephalogram (EEG) or electromyography, as our hospital does not utilize EEG monitoring during ECT. Second, owing to the nature of ECT treatment, which is typically administered over six to eight sessions at intervals of several days, this study focused only on the first and second ECT sessions. This does not account for the gradual increase in shock energy that occurs as the number of sessions increases. Finally, this was a single-center prospective analysis with a relatively small sample size, which limits the generalizability of the results.

Table 1: Patients' clinical-demographic characteristics

Characteristics	Group E (n = 15)	Group R (n = 15)	p
Age	38.1 ± 15.7	40.6 ± 18.1	0.164
Female	10 (67)	10 (67)	1.000
Body weight (kg)	64.4 ± 12.6	67.7 ± 14.3	0.979
Psychiatric diagnosis			
Major depressive disorder	5 (33)	5 (33)	
Schizophrenia	4 (27)	3 (21)	0.968
Schizoaffective disorder	2 (13)	2 (13)	
Bipolar disorder	4 (27)	5 (33)	

Table 2: Shock energy and seizure duration

	Group	Mean	SD	t-test	Level of Significance
Shock Energy (J)	Etomidate	35.0	13.5	0.57	0.288
	Remimazolam	33.7	12.3		
Seizure duration (s)	Etomidate	60.3	37.8	2.04	0.025*
	Remimazolam	47.4	19.7		

SD, standard deviation

Table 3: Recovery time

	Group	Mean	SD	t-test	Level of Significance
Self-respiration recovery time (s)	Etomidate	279.2	92.4	0.781	0.441
	Remimazolam	259.9	105.9		
Eye-opening recovery time (s)	Etomidate	392.1	167.6	1.422	0.166
	Remimazolam	343.8	115.3		

SD, standard deviation

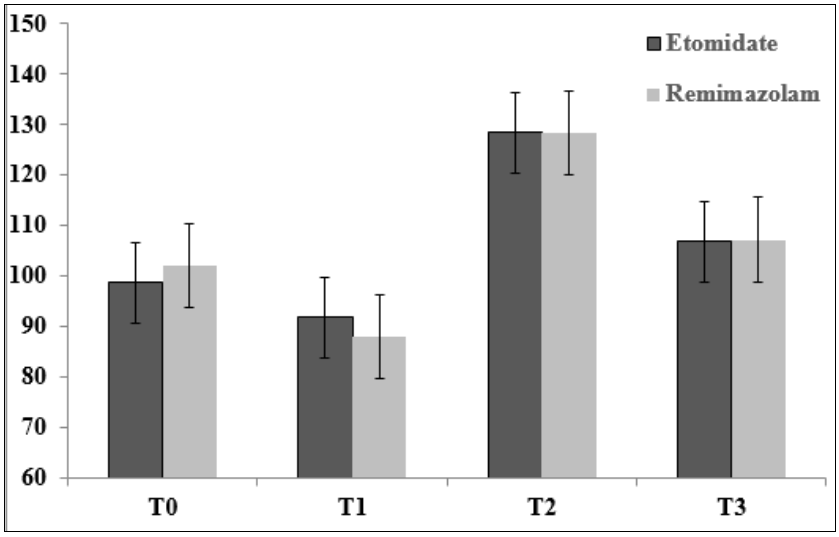

Fig 1: Graph showing variation in mean arterial blood pressure across both groups at different time intervals.

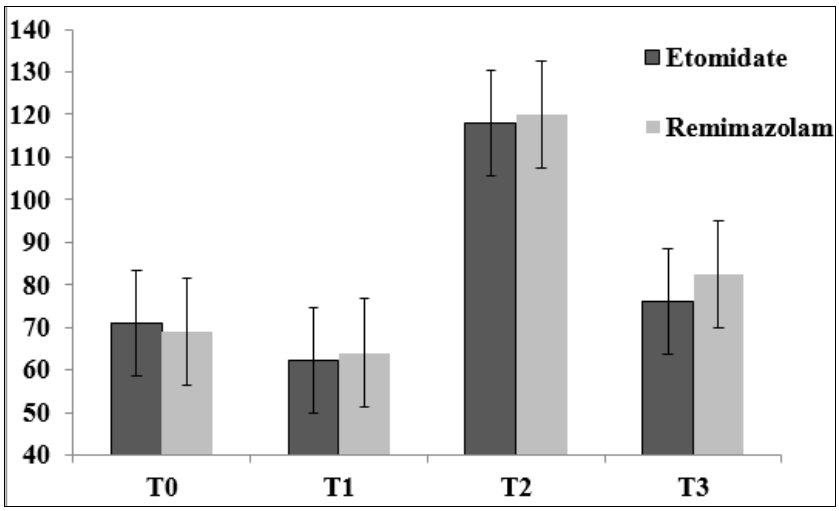

Fig 2: Graph showing variation in heart rate across both groups at different time intervals.

Conclusion

Our study demonstrated that remimazolam can be used as an alternative to etomidate as an ECT-induction agent. There were no significant differences in hemodynamic stability, recovery parameters, or seizure shock thresholds compared with etomidate while inducing seizure durations sufficient for effective treatment. It may be particularly suitable for patients at high risk of adrenal insufficiency, serving as a viable alternative to etomidate.

Acknowledgments

This research was supported by the Department of Psychiatry at Dancook University Hospital. This research received no external funding. The authors declare no conflicts of interest.

References

1. Kerner N, Prudic J. Current electroconvulsive therapy practice and research in the geriatric population. Neuropsychiatry. 2014 Feb;4(1):33-54.
2. Ding Z, White PF. Anesthesia for electroconvulsive therapy. Anesth Analg. 2002 May;94(5):1351-1364.
3. Jaffe R. The practice of electroconvulsive therapy: recommendations for treatment, training, and privileging: a task force report of the American Psychiatric Association, 2nd ed. Am J Psychiatry. 2002;159(2):331.
4. Zahavi GS, Dannon P. Comparison of anaesthetics in electroconvulsive therapy: an effective treatment with the use of propofol, etomidate, and thiopental. Neuropsychiatr Dis Treat. 2014 Feb;10:383-289.
5. Fragen RJ, Shanks CA, Molteni A, Avram MJ. Effects of etomidate on hormonal responses to surgical stress. Anesthesiology. 1984 Dec;61(6):652-656.
6. Sneyd JR. Remimazolam-current status, opportunities and challenges. Anesthesiol Perioper Sci. 2023 Jul;1(3):25.
7. Hu B, Zhang M, Wu Z, Zhang X, Zou X, Tan L, et al. Comparison of remimazolam tosilate and etomidate on hemodynamics in cardiac surgery: A randomised controlled trial. Drug Des Devel Ther. 2023 Feb;17:381-388.
8. Oh EJ, Chung YJ, Lee J-H, Kwon EJ, Choi EA, On YK, et al. Comparison of propofol vs. remimazolam on emergence profiles after general anesthesia: A randomized clinical trial. J Clin Anesth. 2023 Nov;90:111223.
9. Boylan LS, Haskett RF, Mulsant BH, Greenberg RM, Prudic J, Spicknall K, et al. Determinants of seizure threshold in ECT: Benzodiazepine use, anesthetic dosage, and other factors. J ECT. 2000 Mar;16(1):3-18.
10. Trzepacz PT, Weniger FC, Greenhouse J. Etomidate anesthesia increases seizure duration during ECT: A

retrospective study. Gen Hosp Psychiatry. 1993 Mar;15(2):115-120.
11. Shah A, Wadoo O, Latoo J. Electroconvulsive therapy (ECT): important parameters which influence its effectiveness. Br J Med Pract. 2013 Dec;6(4):a634.
12. Tess AV, Smetana GW. Medical evaluation of patients undergoing electroconvulsive therapy. N Engl J Med. 2009 Apr;360(14):1437-1444.
13. Weinger MB, Partridge BL, Hauger R, Mirow A. Prevention of the cardiovascular and neuroendocrine response to electroconvulsive therapy: I. effectiveness of pretreatment regimens on hemodynamics. Anesth Analg. 1991 Nov;73(5):556-662.

How to Cite This Article
Kwon MA, Song J, Ji S, Yun Y, Lee W. Comparison of remimazolam and etomidate as induction agents for electroconvulsive treatment. International Journal of Medical Anesthesiology. 2024; 7(4): 169-174.