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Research Paper

Atracurium as an Alternative to Succinylcholine in Electroconvulsive Therapy: A Randomized Clinical Trial

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ABSTRACT

Background: Electroconvulsive Therapy (ECT) is a successful treatment option for various psychiatric disorders. It is performed under general anesthesia where succinylcholine is the preferred muscle relaxant in this process. However its several contraindications and potential adverse effects, and the fact that it is not always available should be considered. Therefore, finding an effective and safe alternative is crucial.

Objectives: This study aims to assess the safety and efficacy of atracurium in ECT.

Materials & Methods: This single-blind clinical trial was conducted at Shafa hospital affiliated to Guilan University of Medical Sciences from November 2020 to April 2021. Participants were 67 eligible patients with ECT, randomly assigned into two groups receiving succinylcholine (0.5 mg/kg), and atracurium (0.2 mg/kg). Seizure duration, hemodynamic parameters, the time to return to spontaneous breathing, and recovery time were assessed and compared between the two groups.

Results: Seizure duration was longer in the succinylcholine group (P=0.071), while the time to return to spontaneous breathing (P=0.0001) and the recovery time (P=0.0001) were significantly longer in the atracurium group. The trend of changes in the Mean Arterial Pressure (MAP) and Heart Rate (HR) were significant over time; however, the difference between the two groups was significant only in HR one minute after the seizure induction (P=0.001). None of patients was reported serious adverse effects.

Conclusion: When succinylcholine can't be used, atracurium can be a safe alternative in the ECT process.

Keywords: Atracurium, Electroconvulsive therapy, Succinylcholine

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Highlights

- Electroconvulsive Therapy (ECT) is a therapeutic method in psychiatry particularly in patients resistant to treatments.
- Anesthesia management of ECT patients is challenging. Succinylcholine is known as the preferred drug for this process, but it has several contraindications.
- Atracurium can be a safe alternative to succinylcholine in the ECT process when succinylcholine is contraindicated.

Introduction

Electroconvulsive Therapy (ECT) has been widely used as a treatment option in psychiatry, particularly in conditions such as resistant to psychopharmacological treatments, risk of suicide, and any situations with the need for urgent therapeutic response [1-5]. During the procedure, a series of generalized epileptic seizures are induced in the patient under general anesthesia [6-8]. Although ECT is classified as a low-risk procedure, anesthesia management in these cases can be associated with several challenges [9-14]. Prior to anesthesia interventions, this treatment was not considered proper for humans. Anesthesia is a safe method and causes easier management of high-risk medical patients [15, 16]. An anesthesiologist should be familiar with the potential complications of ECT and its physiological effects on the cardiovascular and nervous systems. Proper cooperation between psychiatrist and anesthesiologists is also essential [9, 17, 18]. Although anesthesia management involves hypnotic and muscle relaxant agents, is not the same for specific patients and sometimes varies according to their conditions [19].

In ECT, administration of muscle relaxants is essential to prevent joint dislocations, bone and teeth fractures, and injuries [20, 21]. Succinylcholine has been known as the preferred muscle relaxant in ECT, because it acts in a short duration which commensurate with the time of ECT [22]. However, succinylcholine has some disadvantages; it causes pseudocholinesterase deficiency, allergy to drugs, malignant hyperthermia, Brugada syndrome, and burns in patients [23, 24]. Case reports have indicated prolonged apnea following succinylcholine administration for ECT along with acquired or genetic pseudocholinesterase deficiency [25-29]. They have emphasized the necessity of providing alternatives for succinylcholine in order to prevent interruption in the treatment process. In addition to several contraindications and potential adverse effects, the fact that this drug is not always available should also be considered.

Given that ECT is the only treatment option in some cases, a safe and effective alternative should be considered for the patients with succinylcholine contraindication. Mivacurium has been proposed with promising results; however, it also causes pseudocholinesterase deficiency. On the other hand, similar to many other useful and even essential drugs, it is not available in Iran [23]. The combination of rocuronium and sugammadex has also been successfully administrated in these cases; however, they are also not always available or are expensive [24]. To date, there have been scant sporadic studies, mostly case reports, on the use of atracurium as a safe, cost-effective, and available drug in ECT. However, to the best of our knowledge, no coherent clinical trial has been performed in this field. Therefore, this study aims to evaluate the safety and efficacy of atracurium in ECT patients compared to succinylcholine as a conventional drug.

Materials and Methods

Research design and participants

After approval by the Research Ethics Committee of Guilan University of Medical Sciences, this single-blind clinical trial was conducted at Shafa hospital, Rasht, Iran from November 2020 to April 2021. Psychiatric patients aged >18 years, candidate for ECT based on the American Society of Anesthesiologists (ASA) physical status classifications I & II and declared informed consent were selected for the study. Patients with difficult mask ventilation predictors, Body Mass Index (BMI) ≥30 kg/m^2, Mallampati classification III or IV, age ≥57 years, severely limited mandibular protrusion, a history of snoring, any contraindication for atracurium such as systemic mastocytosis, high amount of magnesium in the blood, myasthenia gravis, skeletal muscle disorders, history of asthma, allergies, and with the need for tracheal intubation or any urgent intervention were excluded from the study.

An anesthesia technician who was blind to the study process performed the allocation using the randomization quadruple blocks with a ratio of 1:1 for two groups of

succinylcholine and atracurium in the Sealed Envelope. Due to the differences between the properties of muscle relaxants such as succinylcholine-related fasciculation and the required time before delivering stimulus in atracurium group, the observer who documented the data could not be blinded to the study group.

Anesthesia management and the procedure

The patients were fasted for at least 6-8 hours and were visited by the responsible anesthesiologist before receiving the procedure. In order to prevent bradycardia and salivation, atropine sulfate (0.01 mg/kg IM) was administrated 30 minutes prior to the procedure. After arrival of patients to the ECT ward, routine standard monitoring methods including electrocardiogram, peripheral Oxygenation Saturation (SpO_2) monitoring, and noninvasive blood pressure monitoring were performed, and a 20-gauge cannula was used to secure intravenous access. Propofol was used for anesthesia induction due to its favorable hemodynamic effects and rapid onset and redistribution. After induction of anesthesia with 1 mg/kg propofol, confirmation of proper mask ventilation, non-response to verbal command, and lack of eyelash reflex, 0.5 mg/kg succinylcholine (500 mg/10 mL, Caspian Tamin Co, Iran) for one group and 0.2 mg/kg atracurium (50 mg/mL, Caspian Tamin Co, Iran) for another group were administrated. These dosages were chosen based on previous studies [30, 31].

Firstly, the patient was passively pre-oxygenated using a face mask followed by active hyperventilation at a rate of 40-50 breaths per minute. Prior to the seizure induction, bi-temporal electrodes and a mouth guard were placed; then, a brief grand-mal seizure was produced (PM-ES21881SOMATICS, LLC Lake Bluff, IL, USA, Class I, Type BF). In this process, 70-120 volts were applied to result in approximately 800 milliamperes of direct current for a duration of 100 milliseconds to 6 seconds. At the end of the seizure induction, the mouth guard was replaced with an airway with appropriate size, and face mask ventilation was started until spontaneous breathing returned. In the atracurium group, the patient was ventilated at least for three minutes before seizure induction, and a bolus dose of 0.2 mg/kg propofol was injected 30 seconds prior to stimulation. At the end of the procedure, atropine 0.02 mg/kg and neostigmine 0.04 mg/kg were used to reverse the effects of muscle relaxants.

Measurement point times and outcomes

Hemodynamic parameters including Heart Rate (HR) and Mean Arterial Pressure (MAP) were recorded before induction of anesthesia (T0), one minute after the seizure (T1), and 15 minutes after induction of anesthesia (T2). The duration of seizure was determined based on clinical observation of colonic movements in the isolated limb using a stopwatch. Any adverse effects were also recorded by the responsible resident of anesthesiology during the ECT process and after discharge. After full consciousness and effective breathing, the patients were transferred to the recovery ward. They were discharged after obtaining a score of 10 based on the Aldrete scoring criteria. Aldrete's scoring system is a commonly used scale for determining when individuals can safely be discharged from the post-anesthesia care unit. The duration of seizure, the time to return spontaneous breathing, and the time of discharge (recovery) were compared between the two groups. It should be noted that, during the procedure, the anesthesia team were prepared to manage any emergency situations such as hemodynamic disturbances, arrhythmia, and drop in oxygen saturation.

Statistical analysis

To analyze the collected data in SPSS software v. 21, chi-square test, Fisher's exact test, t-test, and repeated measurement Anova were used. A P-value less than 0.05 was considered as the significance level. The parametric data were described as Mean±SD and nonparametric data were described by median (range).

Results

A total of 67 patients with a Mean±SD age of 45.1±13.53 years participated in this study divided into two groups of Atracurium (n=32) and Succinylcholine (n=35), which 53.71% were male and 46.3% were female. Based on ASA classification system, 83% of them were in class I and 16.4% in class II. Their Mean±SD BMI was 24.78±2.7 kg/m^2. In terms of psychiatric diagnosis, 52.2% had psychosis, 34.3% bipolar disorder, and 13.4% major depression. Patients' demographic characteristics in the two groups are shown in Table 1, where the results showed no significant difference between the groups in terms of these characteristics (P>0.05).

As shown in Table 2, seizure duration was longer in the succinylcholine group (6.4±24.45 seconds) compared to the atracurium group (6.35±21.59 seconds), but there was no significant difference (P=0.071). The time to re-

Table 1. Demographic characteristics of participants

Variables		No. (%)/Mean±SD			P
		Atracurium	Succinylcholine	Total	
		N	N	N	
Gender	Male	17(53.1)	19(54.3)	36(53.7)	0.924
	Female	15(46.9)	16(45.7)	31(46.3)	
Age (y)	≥60	27(84.4)	32(91.4)	59(88.1)	0.646
	>60	5(15.6)	3(8.6)	8(11.9)	
		45.06±14.07	45.14±13.24	45.1±13.53	0.981
ASA class	I	27(84.4)	29(82.9)	56(83.6)	0.867
	II	5(15.6)	6(17.1)	11(16.4)	
BMI		24.4± 2.42	25.13±2.92	24.78±2.7	0.27

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turn to spontaneous breathing was significantly longer in the atracurium group) 21.03±3.81 seconds (compared to the succinylcholine group) 9.2±3.1 seconds ((P=0.0001). The recovery time was also significantly longer in the atracurium group (24.12±6.4 minutes) compared to the succinylcholine group (18.37±4.72 minutes) (P=0.0001).

Two groups were also compared regarding hemodynamic parameters including HR and MAP (Table 3). In both groups, the trend of changes was significant from T0 (before induction of anesthesia) to T2 (15 minutes after induction of anesthesia) (P=0.0001). However, the difference between groups was significant only in HR at T1 (P=0.001).

The frequency of adverse effects was not significantly different between the two groups (P=0.86). And none of them reported serious adverse effects. Three patients in the succinylcholine group developed bradycardia during the procedure, which rezoned well to a single dose of atropine 0.5 mg. Two patients in the succinylcholine group complained of headaches. Moreover, two patients in the atracurium group and 4 in the succinylcholine group experienced myalgia after the procedure (Table 4).

Discussion

Over the years, when succinylcholine was contraindicated and ECT was the only therapeutic option, the condition has been challenging for both anesthesiologists and psychiatrists. In this situation, different decisions are made by the anesthesia team with hesitation. In some cases, when succinylcholine is administrated with risk acceptance or atracurium is used without precise dosage, there may be

Table 2. Comparison of seizure duration, time to return to spontaneous breathing, and recovery time between the two study groups

Variables	Groups	n	Mean±SD	P
Seizure duration (second)	Atracurium	32	21.59±6.35	0.071
	Succinylcholine	35	24.45±6.4	
Time to return to spontaneous breathing (minute)	Atracurium	32	21.03±3.81	0.0001
	Succinylcholine	35	9.2±3.1	
Recovery time (minute)	Atracurium	32	24.12±3.6	0.0001
	Succinylcholine	35	18.37±4.72	

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Table 3. Comparison of hemodynamic parameters between the two groups

Groups		Before Anesthesia	1 min After Seizure	15 min After Anesthesia	P	P
HR (bpm)	Atracurium	88.87±13.33	107.96±12.7	84.75±11.93	0.0001	0.0001
	Succinylcholine	4.83±11.16	94.118±14.2	51.88±8.95	0.0001	
	P	0.072	0.001	0.147		
MAP (mmHg)	Atracurium	93.28±11.21	102.28±13.12	95.71±13.39	0.0001	0.075
	Succinylcholine	89.74±9.9	103.8 ±13.27	93.05±10.31	0.0001	
	P	0.175	0.64	0.36		

insufficient relaxation or sometimes prolonged apnea. Or when the procedure is performed without muscle relaxants, the patient may experience intolerable muscle pain due to severe muscle contractions. On the other hand, succinylcholine may no longer available for a long period in Iran due to sanctions. Therefore, this research was conducted to address these problems at Shafa hospital, Rasht, Iran. To our knowledge, this is the first study that examines the possibility of replacing succinylcholine with atracurium under certain conditions. Similar research in this field is so limited; most of them are case reports.

During the ECT process, a brief parasympathetic stimulation is followed by sympathetic response which significantly increases HR and MAP. In this regard, various drugs are used to blunt these fluctuations [18, 32]. In this study, hemodynamic parameters were assessed as an important outcome that could be influenced by anesthesia regimes and patients' conditions. There was no significant difference in hemodynamic status between the two groups, except in HR which was significantly higher in the group received succinylcholine at T1 (one minute after the seizure). Although the trend of changes in HR and MAP values over time (from T0 to T2) was significant, the mean values were almost in the normal range. This stable situation reflects the acceptable performance and proper coordination of the responsible medical team, psychiatrists, and anesthesiologists involved in the ECT process. The patients were visited by the responsible anesthesiologist prior to the procedure; then, they were scheduled to receive ECT in optimal conditions. Appropriate medications and dosage were prescribed according to the medical conditions of each patient and the procedure was performed under standard monitoring.

In both study groups, the mean seizure duration was at the acceptable range, slightly higher in the succinylcholine group, but there was no significantly difference between them. The optimal therapeutic seizure is when both robust electroencephalogram expressions and motor seizure last for at least 20 seconds; the main therapeutic effects occur during motor seizures. However, it cannot be an disadvantage of this study, because the current evidence suggests that the most important determinants of seizure efficacy are clinical treatment outcomes and patient recovery rate. Other study factors in our study were the time to return to spontaneous breathing and the recovery time, which were significantly longer in the atracurium group; this was expected due to the pharmacokinetics of the used drugs. In terms of clinical complications, none of the patients in our study were affected by severe

Table 4. Comparing the frequency of adverse effects between the two groups

Complications	No. (%)			P
	Atracurium	Succinylcholine	Total	
Bradycardia	0(0)	3(9.4)	3(4.5)	0.104
Headache	0(0)	2(5.7)	2(3)	0.49
Myalgia	2(2.6)	4(11.4)	6(9)	0.675

adverse effects of drugs and no significant difference was observed between the two groups in this regard.

Kramer et al. in a case report presented prolonged apnea in a patients with cholinesterase deficiency who underwent ECT using succinylcholine as a muscle relaxant. They emphasized the need for a safe alternative to this conventional muscle relaxant agent [25]. Lui et al. used atracurium as a muscle relaxant in ECT patients at two doses of 0.3 and 0.5 mg/kg. They believed that other muscle relaxants should be investigated due to several unwanted side effects of succinylcholine including myalgia, increased intracranial, intra-abdominal pressure, and hyperkalemia [31]. Nazemroaya et al. compared the effects of cisatracurium with succinylcholine in ECT patients in terms of seizure duration and hemodynamic changes. They concluded that cisatracurium can be a viable alternative [33]. In our study, we used atracurium due to shorter duration of action. Kadar et al. reported the successful management of a patient with a history of malignant hyperthermia with rapacuronium [34]. Hoshi et al. compared the recovery time of patients after using rocuronium-sugammadex and succinylcholine. They found that the combined drug was a better alternative. They declared that succinylcholine has several adverse effects and it is crucial to find an alternative to it [35]. Nishiyamaet al. assessed the efficacy of vecuronium as a muscle relaxant during ECT. They found that seizure duration was significantly affected by this drug compared to succinylcholine [36]. In another study, Setoyama et al. used vecuronium instead of succinylcholine in a patient with a history of neuroleptic malignant syndrome. Although the patient was safety and successfully managed, the duration of anesthesia reached to 38 minutes [37, 38].

Overall, the current study revealed that the succinylcholine-related adverse effects and contraindications when the psychiatric patients' only treatment option is ECT is a challenging issue with no comprehensive solution. We hope that the promising findings of this clinical trial can help safety manage ECT patients without interruption in the treatment process. As one of the limitations of this study, patients' seizures were evaluated solely based on the researcher's observation, and electroencephalogram was not used to examine brain waves.

Conclusion

Low doses of atracurium can be a safe and available alternative to succinylcholine with fewer adverse effects. This is a valuable finding in a developing country with limited drug availability. However, due to long duration of return to spontaneous breathing and recovery, it should be considered only for certain conditions. Further clinical trials are recommended to find practical results that can be generalized to clinical practice.

Ethical Considerations

Compliance with ethical guidelines

All study procedures were in compliance with the ethical guidelines of the Declaration of Helsinki 2013. The study protocol was approved by the Ethics Committee of Guilan University of Medical Sciences (Code: IR.GUMS.REC.1399.323) and was registered by the Iranian Registry of Clinical Trials (ID: IRCT20170314033069N2). Informed consent was obtained from all participants.

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Authors' contributions

Conceptualization: Abbas Sedighinejad and Gelareh Biazar; Investigation and Resources: Robabeh Soleimani, Mohammad Haghighi and Siamak Rimaz; Writing-original draft: Seyed Mahmood Rezvani and Hossein Khoshrang ; Data collection: Seyed Mahmood Rezvani; Methodology: Soheil Soltanipour; Writing-review & editing: Gelareh Biazar, Mohammad Haghighi, and Robabeh Soleimani; Supervision: Abbas Sedighinejad and Siamak Rimaz.

Conflict of interest

The authors declared no conflicts of interest.

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