RESEARCH ARTICLE

Comparison of Seizure Duration and Hemodynamic Changes with Cisatracurium versus Succinylcholine in Electroconvulsive Therapy

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Background: In patients undergoing electroconvulsive therapy (ECT), succinylcholine is routinely used as a muscle relaxant. Occasionally, cisatracurium is used on a limited basis in this regard. The present prospective randomized study is designed to compare cisatracurium and succinylcholine for their effect on cardiovascular changes, seizure duration, and recovery after ECT on patients undergoing ECT.

Methods: This study was a randomized double-blind clinical trial without controls conducted on 64 patients, who were candidates for receiving ECT. Bipolar mood disorder as a coexisting medical condition in 32 patients (50%) had the highest prevalence. Consequently, patients were randomly divided into two groups namely, group C (n= 32, cisatracurium 50 mcg/kg), and group S (n = 32, succinylcholine 2 mg/kg-1).

Blood pressure, heart rate (HR), O2 saturation (Spo2) and seizure duration were measured in each group. The data were compared using independent t-test and chi-square tests.

Results: Both groups were comparable in gender, weight, American Society of Anesthesiologists (ASA) physical status, with no statistically significant differences ($p > 0.05$). The systolic blood pressure (SBP) in 1 minute after the end of shock was significantly higher in the C group, than the S group. In addition, HR was also higher in the fifth minute (5th) in the C group compared to the S group. The mean percentage of Spo2 at the time before the seizures, the first minute (1st) and 5th minutes in the C group, was higher than the S group. There was a significant difference ($p=0.001$) between the seizure duration in the C group (36.72 ±6.09 seconds), compared to the S group (27.37 ±4.99 seconds).

Conclusion: Although cisatracurium is considered a muscle relaxant with intermediate duration of action, its low-dose administration in ECT is not only without any limitations, but may also be a more appropriate alternative to succinylcholine. On the other hand, if the duration of seizure is less than 20 seconds in ECT, it will no longer be an effective treatment, as a result, since cisatracurium increases the seizure duration, it could have better therapeutic effects in ECT.

Keywords: cisatracurium; succinylcholine; seizure duration; electroconvulsive therapy; hemodynamic changes

Electroconvulsive therapy (ECT) is an effective treatment for a variety of psychiatric disorders, including bipolar disorder, major depression, schizophrenia etc., and especially in cases where drug therapy has failed [1].

In ECT, a brief electrical current is applied to the patient, under general anesthesia, which induces a generalized tonic-clonic seizure in the patient. The duration of this seizure should be at least 20 seconds and the duration of the clonic phase should be at minimum, 15 seconds to be considered effective for ECT [2-4].

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Seizure parameters, including the duration of the seizure, are important factors in the effectiveness of ECT. On the other hand, the seizure is affected by various factors, such as anesthetic and muscle relaxant medications. It seems that the evaluation of these parameters is important in using and comparing different anesthetic and muscle relaxant medicines and choosing the suitable drug from the available drugs for anesthesia in ECT [5-7]. In ECT, an anesthetic followed by a muscle relaxant is routinely used to reduce muscle contractions and to prevent joint dislocations, reduce possible fractures and cause less injury [8]. Muscle relaxants are classified as depolarizing neuromuscular blockers and nondepolarizing neuromuscular blockers(NMBDs). The mechanism of action, metabolism, and complications of these two groups are important factors in choosing these medicines in ECT [9]. All NMBDs contain quaternary ammonium compounds and as such, are closely related structurally to acetylcholine. Positive charges at the quaternary ammonium sites of NMBDs mimic the quaternary nitrogen atom of acetylcholine. In addition, populations of neuronal nicotinic and muscarinic receptors

are located pre-junctionally at the neuromuscular junction [10]. Succinylcholine is used as a muscle relaxant in ECT and is categorized as short acting in terms of its duration of action [11-12]. Succinylcholine-induced cardiac dysrhythmias are prevalent and varied in type. The drug stimulates cholinergic autonomic receptors on both sympathetic and parasympathetic ganglia and muscarinic receptors in the sinus node of the heart. At low doses, both negative inotropic and chronotropic responses may occur [13]. With large doses of succinylcholine, these effects may become positive, causing tachycardia [14]. When succinylcholine is used, the depolarization process increases plasma potassium levels. Usually, this increase is in the range of 1-2 mEq/l but there are reports of increases of more than 4 mEq/l of potassium in some patients with non-traumatic neuromuscular diseases, which may cause arrhythmias and cardiopulmonary collapse [15-16]. In spite of its many adverse effects, succinylcholine remains commonly used. Its popularity is likely the result of its rapid onset of effect, the profound depth of neuromuscular blockade it produces, and its short duration of action. Despite the fact that, succinylcholine may not be used as regularly as in the past for routine endotracheal intubation, but it is still a muscle relaxant for rapid-sequence induction of anesthesia. Although, 1.0 mg/kg of succinylcholine is recommended to facilitate endotracheal intubation at 60 seconds, as little as 0.5 to 0.6 mg/kg allows for adequate intubating conditions 60 seconds after administration [17]. The use of succinylcholine in cases such as pseudo-choline esterase enzyme deficiency, cholinesterase inhibitors, and severe neuromuscular diseases can increase the risks of performing electrotherapy in some patients [18]. Cisatracurium is the right-hand isomer of atracurium [19]. Cisatracurium and atracurium are both non-depolarizing neuromuscular blockers. Cisatracurium, the 1R cis–1′R cis isomer of atracurium, comprises approximately 15% of atracurium by weight but more than 50% in terms of neuromuscular blocking activity [11]. Cisatracurium creates less histamine release, while histamine release is the major complication of atracurium [20-21]. The drug is transformed to ladanosine in the plasma by Hoffman elimination and further metabolized into a number of conjugated metabolites [22-24].

Methods

This study was a double-blind clinical trial with no control group and was performed (enrolment period Oct 2016 to Jan 2017) in patients referred to AL Zahra Hospital's Psychiatric Department for Children and Adolescents who were candidates for electroconvulsive therapy. A consent form was obtained from the parents for the patients' participation in this study.

Inclusion criteria: All patients under 25 years old, admitted to Al-Zahra Hospital, who were classified as ASA1, and were candidates for ECT. Alcohol and drug addiction, severe allergies, previous history of seizures and convulsions, patients with an unstable medical condition.

Exclusion criteria: Patients with seizure induced by an electroshock device for more than 90 seconds and less than 20 seconds, patients who needed to have endotracheal intubation and those who had cardiopulmonary arrest were excluded from the study.

This study was registered in the Iranian Registry of Clinical Trials (IRCT) at www.irct.ir with an identification registration code: IRCT2016081229310N1.

Patients were divided into two groups, each with a sample size of 32, with two drug packages, A and B, prepared. The A package included cisatracurium (50 mcg/kg) and sodium thiopental (2 mg/kg) and the B package contained succinylcholine (0.5 mg/kg) and sodium thiopental (2 mg/kg). All patients had been clinically examined including routine physical examination and blood sampling. The variables investigated in this study included systolic blood pressure(SBP), diastolic blood pressure(DBP), mean arterial pressure(MAP), saturation of peripheral oxygen(Spo2), heart rate(HR) and seizure duration. In all cases under investigation, baseline BP, HR, and Spo2 were measured before undergoing ECT. None of the patients received any premedication. Preoperative preparation procedure, NPO time (all patients were fasted for over 6 h) and fluid therapy based on body weight, were similar in all patients. Then electrocardiography (ECG), pulse oximeter, sphygmomanometer (to assess SBP, DBP and MAP) devices were attached to patients. The pulse oximeter and sphygmomanometer were not applied to the same arm because of interactional disturbances. ECT electrodes were applied on both sides of the head on temporal regions. After all the patients received bilateral ECT, the BP, HR, Spo2 variables were measured and recorded in respective checklists at 0,1, 5, and 10 minutes after ECT induction. A pulsewidth machine (Thymatron System IV; Somatics LLC, Lake Bluff, IL) with a 0.5-ms brief pulsewidth was used. The frequency of the pulse wave was 70Hz.

The duration of seizure was measured using a chronometer and recorded. The method of assigning patients to intervention groups was simple randomization, and sampling method was simple or easy. For blinding purposes, the primary anesthesiologist was responsible for patient randomization and induction of general anesthesia while the other investigator (unaware of group allocation) was responsible for data collection. For the purpose of double blinding, patients were also kept unaware of group allocation. The collected data were analyzed by SPSS software, version 20, using Chi-square, Fisher's exact test, ANOVA for repeated observation and independent T-test. The significance level was considered less than 0.05.

Results

Based on the results, there were no significant differences among the groups in most cases in terms of effects on cardiovascular system variables, seizure variables, and cognitive function. However, in cases where differences are statistically significant between the two groups (at 95%), the results are presented.

Effects of cisatracurium versus succinylcholine in ECT on hemodynamic system parameters (HR, BP, and Spo2) and seizure variables were recorded at 0, 1, 5, and 10 minutes after ECT induction, were used in this evaluation, and results presented below in three segments.

Characteristics of the patients

64 patients who fit the inclusion criteria for this study by psychiatric diagnosis were divided as follows: 32 patients were anesthetized with sodium thiopental and muscle relaxant (cisatracurium) during ECT and another 32 patients with sodium thiopental and muscle relaxant

(succinylcholine). The groups were named C for cisatracurium and S for succinylcholine. We have studied 64 patients of both genders, less than 25 years old referred for ECT.

According to (Table 1), the C group consisted of 16 boys and 16 girls with the average age of 13.15 ± 3.36 years. The S group consisted of 9 boys and 23 girls with an average age of 14.2±1.16 years, which were statistically similar in age and gender (P> 0.05). In addition, bipolar mood disorder as a coexisting medical condition in 32 patients (50%) had the highest prevalence and the least prevalence was observed in diseases such as mental retardation, schizophrenia, depression, and anxiety with a frequency of 2 cases (3.1%).

Table 1- Distribution of gender and type of diseases between two groups

		Frequency (%)		Total	P-Value*
		Group C	Group S		
Gender	F	(25%)16	(35.9%)23	(60.9%)39	0.127
	M	(25%)16	(14.1%)9	(39.1%)25	0.128
Age		13.15±3.36	14.12±1.16	14.2±1.70	
Type of diseases	BD	(59.3%)19	(40.6%)13	(50%)32	0.750
	Psychosis	(6.2%)2	(25.0%)8	(15.6%)10	
	ADHD	(6.2%)2	(15.6%)5	(10.9%)7	
	OCD	(12.5%)4	(3.1%)1	(7.8%)5	
	CD	(12.5%)4	(0%)0	(6.2%)4	
	MR	(6.2%)2	(3.1%)1	(4.6%)3	
	Depression	(0%)0	(6.2%)2	(3.1%)2	
	Schizoid	(0%)0	(6.2%)2	(3.1%2	
	anxiety	(0%)0	(6.2%)2	(3.1%)2	
	MR	(6.2%)2	(3.1%)1	(4.6%)3	
Total		(100%)32	(100%)32	(100%)64	

*Independent t-test
F, Female; M, Male; BD, Bipolar disorder; OCD, obsessive compulsive disorder; CD, Conductive disorder; MR, Mental retardation; ADHD, Attention-deficit/hyperactivity disorder

Hemodynamic changes

In addition, comparison of the average of SBP, DBP, MAP, HR and Spo2, was performed in the time before seizure occurrence, 1, 5 and 10 minutes after the seizure in each of the two groups, which is shown in (Table 2). Moreover, the SBP in 1 minute after the end of shock was significantly higher in the C group, than the S group with a mean of 125.52 ± 10.16 mmHg, and 119.28 ± 11.13 mmHg, respectively(P=0.021). Moreover, DBP, in the time before seizure, was significantly less in the C group with a mean of 74.97 ± 9.62 mmHg, compared to the S group with a mean of 80.81 ± 12.72 mmHg (P=0.040). Patients' heart rate was also higher in the first minute in the C group with a mean of 106.00 ± 15.72 beats per minute (BPM) compared to the S group with a mean of 97.38 ± 16.13 BPM (p=0.033). It was also significantly higher in the 5th minute, in the C group with 111.21 ± 15.58 BPM compared to the S group with a mean of 96.69 ± 17.97 BPM (P=0.001). At other times, SBP, DBP, MAP and HR of the patients in the two groups, did not have significant differences (P>0.05).

Table 2- Mean systolic, diastolic, and arterial blood pressure and heart rate in both groups at different times.

	Time	Group C		Group S		P-Value*
		Mean	SD	Mean	SD	
SBP	Before seizure	120.64	10.90	122.90	12.52	0.618
	1st min	125.52	10.16	119.28	11.13	0.021
	5th min	138.12	25.26	132.25	17.21	0.279
	10th min	125.67	13.78	129.72	12.84	0.225
DBP	Before seizure	74.97	9.62	80.81	12.72	0.040
	1st min	84.33	10.76	86.84	12.13	0.380
	5th min	91.88	15.76	90.72	9.53	0.722

Table 2- Mean systolic, diastolic, and arterial blood pressure and heart rate in both groups at different times (Continued).

	Time	Group C		Group S		P-Value*
		Mean	SD	Mean	SD	
DBP	10th min	76.64	8.69	75.91	11.08	0.768
MAP	Before seizure	90.19	8.85	94.75	11.42	0.088
	1st min	98.06	8.09	97.46	9.88	0.857
	5th min	107.29	14.57	104.56	8.66	0.364
	10th min	92.98	7.35	93.84	10.03	0.693
HR	Before seizure	80.21	9.89	76.69	13.19	0.227
	1st min	106.00	15.72	97.38	16.13	0.033
	5th min	111.21	15.58	96.69	17.97	0.001
	10th min	79.24	9.80	81.53	9.02	0.332

*Independent t-test
SBP, Systolic blood pressure; DBP, Diastolic blood pressure; MAP, Mean arterial pressure; HR, Heart rate.

According to (Table 3), the mean Spo2 at the time before the seizure, the 1st and 5th minutes in the C group, was higher than the S group(P=0.002), (P=0.001) and (P=0.001) respectively.

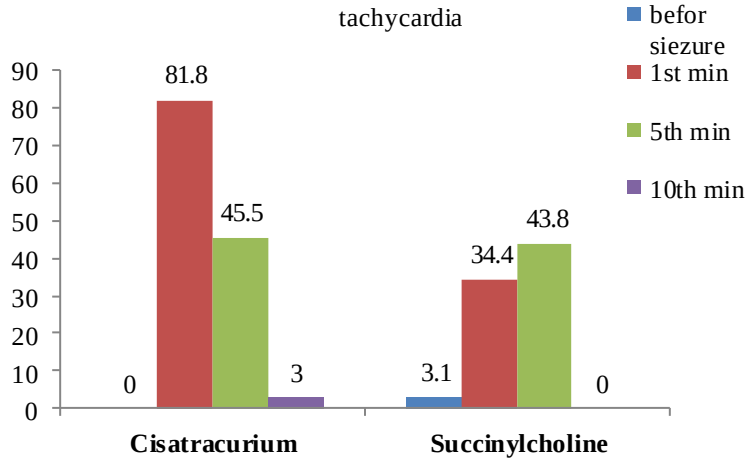
Table 3- Mean Oxygen saturation in the two groups at different times

	Time	Group C	Group S	P-Value*	Time	Group C
		Mean	SD	Mean	SD	
SpO2	Before seizure	97.3	1.57	96.0	0.92	0.002
	1st min	93.36	3.22	88.84	1.93	0.001
	5th min	94.48	2.64	90.28	2.00	0.001
	10th min	96.48	1.60	96.28	1.76	0.628

*Independent t-test
SpO2, peripheral oxygen saturation

On the other hand, the occurrence of tachycardia before the time of the seizure, the 1st, 5th, and 10th minutes of seizures was higher in the C group, than the S group which occurred 81.8% in the cisatracurium and 34.4% in the S group at 1st min aftershocks and finally tachycardia occurred in 3% of cases in the C group but zero cases in the S group (Diagram 1).

Diagram 1- Frequency of incidence of tachycardia in the two groups at different times



Seizure variables

Finally, according to the results of (Table 4), the mean seizure duration was statistically different in the two groups with, 36.72 ± 6.09 seconds in the C group, in comparison with the succinylcholine group with an average of 27.37± 4.99 seconds (P <0.001). On the other hand, the duration of the tonic phase in the C group with a mean of 6.87 ± 1.98 seconds was significantly lower than that of succinylcholine with a mean of 11.59 ± 3.47 seconds (P <0.001). In contrast, the duration of the clonic phase in the cisatracurium group with a mean of29.84 ± 6.55 seconds was significantly longer than S group with a mean of 15.78 ± 5.96 seconds (P <0.001).

Table 4- Comparison of mean seizure duration, tonic and clonic phase between two groups

seizure	Succinylcholine(n=32)	cisatracurium (n=32)	P-Value*
seizure duration	27.37±4.99	36.72±6.09	<0.001
tonic phase	11.59±3.47	6.87±1.98	<0.001
clonic phase	15.78±5.96	29.84±6.55	<0.001

*Independent t-test

Discussion

Anesthetic recovery in ECT is a very important issue with practical implications for psychiatrists who work directly with ECT and for practitioners who prescribe it. The more comfortable the treatment, the better the patients' compliance and satisfaction.

With these goals, in this study the effects of cisatracurium versus succinylcholine on hemodynamic parameters and seizure variables in ECT were studied.

In this research, bipolar disorder had the highest prevalence (50%), while depression had the highest prevalence globally (20%) [25]. In this study, the age of the participants was under 25 years old, whereas in most other studies, the average age of the patients was more than 30. In the Yen study, the average age of the patients was 35 ± 17.8 [26].

According to Table 2, the mean SBP in the first minute in the C group was significantly higher than the S group. In a study by Nazemroaya et al. [27], the mean SBP in the 10th minute in the C group was significantly lower than that of the succinylcholine group. In addition, in this study, the mean SBP in the C group in the first minute, was significantly higher than that of the comparative study, but on the other hand it was significantly higher in the 10th minute in the S group of the corresponding study [27]. The mean DBP after administration of the drug before the seizures was significantly higher in the S group than in the C group. And in the mentioned study, it was significantly higher in the S group, than in the C group [27]. In both studies, the mean DBP increased in the C group between the 1st and 5th minutes, but in comparing the means in the two studies, in the 1st minute, the S group it was significantly less than the C group in the mentioned study, which is not consistent with the present study. In the present study, the mean HR in the 1st and 5th minute in the C group was significantly higher than the S group. However, in the previous study, it was significantly lower in the S group in the stage before seizure occurrence, compared to the C group, which is in agreement with the present study [27]. In this study, the mean SpO2 before the seizure period, the 1st, and the 5th minute in the C group, were higher than the S group, which is also consistent with the previous study [27]. In this study, at the time before seizure occurrence, the 1st, 5th and 10th minutes, more tachycardia complication occurred in the C group compared to the S group, where it occurred in 81.8% of cases at one minute after ending of shock therapy in the C group, compared to, 34.4% in the S group. Finally, at the 10th minute after the end of the shock, it occurred in 3% of cases in the C group while no tachycardia occurred in the S group. But in the comparative study, there was no significant difference between the mean HR in the two groups, while tachycardia was present at all times [27]. In this study, the difference in the mean seizure duration was significantly lower in the S group, than that of the C group. On the other hand, the duration of the tonic phase was significantly lower in the C group, than that of the S group. In the C group, the duration of the clonic phase was significantly higher than in the S group. At the time, we were able to find only one similar study in which cisatracurium and succinylcholine were used simultaneously as muscle relaxants for electroconvulsive therapy [27]. On the other hand, in most anesthetic regimens for ECT, succinylcholine had been used as a muscle relaxant, while in some exceptional cases due to limitations in the use of succinylcholine (such as cholinesterase deficiency), non-depolarizing relaxants such as mivacurium had been used, which were published as case reports [28-29]. In a study performed by Cheam and colleagues, between mivacurium and succinylcholine, mean duration of seizure was 40 seconds in the mivacurium group and 39 seconds in the succinylcholine group. In the present study, the duration of seizure in the C group was significantly higher in the S group, with the average duration of seizure in cisatracurium and mivacurium having no significant difference, but the mean duration of seizure in the succinylcholine was much shorter in this article which did not occur with our study [30]. Also, in the study conducted by Nazemroaya et al. on 67 patients, the mean duration of seizure in cisatracurium was significantly higher than succinylcholine which is consistent with this study [27].

In this study, the duration of the tonic phase in the C group was significantly lower than that of the S group. In a study by Wang et al., 44 patients (19 males and 25 female) were candidates for ECT, where the tonic phase was 8.9 ± 1.5 seconds for men and 9.36 ± 1.35 seconds for women, which was also close to our study in terms of duration. In contrast, in the study, the duration of the clonic phase in the C group was more than that of the S group. In a study by Wang et al., the clonic phase was 17.76 ± 4.71 seconds in men and 19.51 ± 6.04 in women. This was also close to our study, with the exception that the tonic phase of the S group was around two seconds in this article [7]. We hope that this study will help medical professionals to choose the best muscle relaxant for ECT.

Conclusion

Since cisatracurium is an intermediate acting muscle relaxant in terms of duration of action, its low dose administration in ECT not only does not have any limitations compared to succinylcholine, but may even be a

more appropriate alternative. Moreover, if the duration of seizure is less than 20 seconds, ECT will not be effective. Therefore, the use of cisatracurium as a muscle relaxant seems to provide better therapeutic effects than succinylcholine in ECT due to increased duration of the seizure. In addition, a drug like midazolam can be used to provide better cooperation and acceptance of ECT from patients in subsequent sessions and reduction of unwanted side effects. Midazolam, on the other hand, can reduce the duration of seizure, rendering ECT ineffective, but this can be compensated by using cisatracurium, which increases seizure duration compared to succinylcholine. One of the difficulties and limitations of this paper was the limited number of similar studies, which made it impossible to compare this article completely and to discuss it in more detail. Hopefully, in the near future, authors and researchers will strive to resolve these limitations with their work.

Ethical Issues

Ethics committee approval was received for this study from the Ethics Committee of Isfahan University of Medical Sciences (2016/11). In addition, written informed consent was obtained from patients who participated in this study.

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