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Research Article

Comparative Study of the Effect of Midazolam Administration before and after Seizures on the Prevention of Complications in Children Undergoing Electroconvulsive Therapy Compared with a Control Group

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ABSTRACT

Background: One of the complications of ECT treatment is headache. There is a need to use sedation during ECT. As a result, midazolam has been used to address a safe and effective strategy in this regard.

Methods: This study is a double-blind clinical trial that has been performed in three groups: group A, which receives midazolam based on the usual regimen, group B, which receives midazolam after shock, and group C, which is the control group. Patients were asked about headache, nausea, and muscle aches during the recovery time, seizure duration and after becoming fully conscious. Data were analyzed in the PASW version18 software using analysis of variance and repeated measurement tests, ANOVA, independed t and $\chi 2$ tests.

Results: Analysis showed that the frequency of muscle pain after full consciousness in group C was significantly higher than group B, with group B being higher than group A. $\chi 2$ test showed that the frequency of headache, cough and nausea in group C was significantly higher than the two groups A and B.

Conclusion: The result of this research showed that midazolam prodrug plays an effective role in preventing post-ECT complications in children. The effect of midazolam before and after ECT on headache, muscle pain and nausea was investigated and compared with the control group. Also, due to its anterograde amnesia, midazolam can reduce the patient's stress in the next visits, and this issue is even more important when the patient is a child.

In recent years, the use of electroconvulsive therapy or ECT has been considered as a non-pharmacological method effective in the treatment of catatonic patients. This method is now applied to treat severe mental illnesses, especially major depression, bipolar mood disorders, schizophrenia and catatonia. In this method, programmed electrical stimulation of the central nervous system is used to initiate seizures [1-4]. For ECT to be performed in the treatment of pediatric diseases, two electrodes are placed in a specific area of the skull and inducing a general stimulus by passing an electric current through the child's brain between the electrodes [5-7]. This method, like other treatments, may have some side effects [8-9]. These complications are generally divided into two categories; the first category includes dangerous but rare complications and the second includes low-risk but common complications, among which we can mention, a headache [10], nausea and muscle pain [11]. A number of

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risk factors and predictors of preoperative anxiety have been described in children. A history of previous surgery and anesthesia has been reported in this regard. These complications may cause fear of ECT, especially in children [12]. One of the most common complications of ECT treatment, which occurs in almost half of patients treated, is headache [10], which usually peaks 2 hours after ECT, especially in patients under the age of 45, with the amount of headaches being also associated with the duration of the seizure [13-14]. ECT headaches can be treated with drugs such as acetaminophen [15], aspirin [16], nonsteroidal anti-inflammatory drugs and Sumatriptan or beta-blockers and topical methyl salicylate [17]. In some cases, the headache may not respond to the usual analgesic treatments [18-19]. So anesthetic drugs used in ECT include Methohexital, Thiopental, Etomidate, Ketamine, Alfentanil, Propofol, etc. can be considered [11]. Among the various drugs, midazolam is used to maintain anesthesia which has a rapid onset and shorter duration of action. Intravenous injection does not cause pain or phlebitis like all other benzodiazepines. In addition, it possesses hypnotic, amnesic, sedative, and anti-anxiety, anticonvulsant, and central muscle relaxation effects through the GABA system. Midazolam injection is a common method for sedation in these patients [20]. Based on the evidence obtained on the mechanism of action of ECT, it is thought that ECT is effective on the aminobutyric acid neurotransmitter system GABA. As the GABA level rises, the body probably aims to raise the seizure threshold and prevent subsequent complications [21]. Considering that midazolam also increases the seizure threshold through the GABA system and acts like the body's defense system against seizures, it is concluded that this drug can prevent complications after ECT. Also, Midazolam has an amnesia effect, so it can reduce the patient's stress in subsequent visits, and this issue becomes even more important when the patient is a child [12]. So if it is effective on side effects, it can be a reasonable medicine for use in children. According to research, so far no comprehensive study has been done on the effectiveness of midazolam as a premedication on the complications of ECT in children, so the need for this study was felt.

In this study, for the first time, the effect of midazolam on the side effects of electroconvulsive therapy (ECT) in children was investigated. The effect of midazolam administration before and after ECT treatment on headaches, muscle pain and nausea was recorded in comparison with the control group.

Electroconvulsive therapy is the programmed electrical stimulation of the central nervous system to initiate seizure activity. Electrical stimulation firstly generates generalized tonic activity for a few seconds, and subsequently generalized clonic activity which can last from a few seconds to more than a minute [1-2] Electroconvulsive therapy is an effective treatment in a variety of psychiatric diseases including bipolar disorder, major depression and acute schizophrenia, catatonia, especially in cases where drug therapy has failed, or it is considered as a selective treatment in patients requiring a rapid response [1, 3-4]

According to studies, seizure parameters such as seizure length are important in electroconvulsive therapy effectiveness, which appear to be influenced by the type of anesthetic and muscle relaxant drugs [5-7]. Muscle relaxants are divided into two groups of non-depolarizing drugs and depolarizing drugs. Succinylcholine has been found to release large amounts of potassium from skeletal muscle in patients who have burns, muscle trauma, central nervous system trauma, spinal cord injury, peripheral nervous system damage, and muscle changes due to chronic inactivity [8-15]. An increase in potassium levels can cause problems in these patients, including ventricular arrhythmias and cardiac arrest. Cisatracurium and atracurium both act as non-depolarizing neuro-muscular blocking agents, however, cisatracurium as a muscle relaxant is about three times stronger than atracurium. Cisatracurium is often used in anesthetics to facilitate endotracheal intubation as well as a muscle relaxation in maintaining anesthesia in various surgeries, and in addition, it releases less histamine, which is a major complication atracurium usage [16-18]. Considering the fact that few studies have been performed in anesthesia on cardiovascular changes and increased serum potassium levels in electroshock therapy, and the duration of seizure, the results may help to improve this type of treatment.

Methods

The present study was double-blind clinical trial that was conducted during 1397-98 in Al-Zahra Educational and Medical Center of Isfahan (Child and Adolescent Psychiatry) after selecting the patients and obtaining their legal guardian's consent to participate in the study. Inclusion criteria were patients aged 6 to 18 years, with an American Society of Anesthesiologist (ASA) score of 1 and 2.

Criteria for non-admission were patients who required intubation, who were not hemodynamically stable, or who had major diseases such as asthma, drug allergies, neuromuscular diseases, epilepsy, hypertension, and cardiovascular disease. Exclusion criteria included individuals with seizures of less than 20 and more than 90 seconds and those with intubation and refusal of the patient's guardian to continue the study.

Beforehand, approval from Ethics Committee (IR. MUI.REC.1398.587) of the University and informed consents was obtained from the patients or the legal guardians were obtained. The study was listed at

www.irct.ir with a documentation code of IRCT (IRCT20160307026950N16).

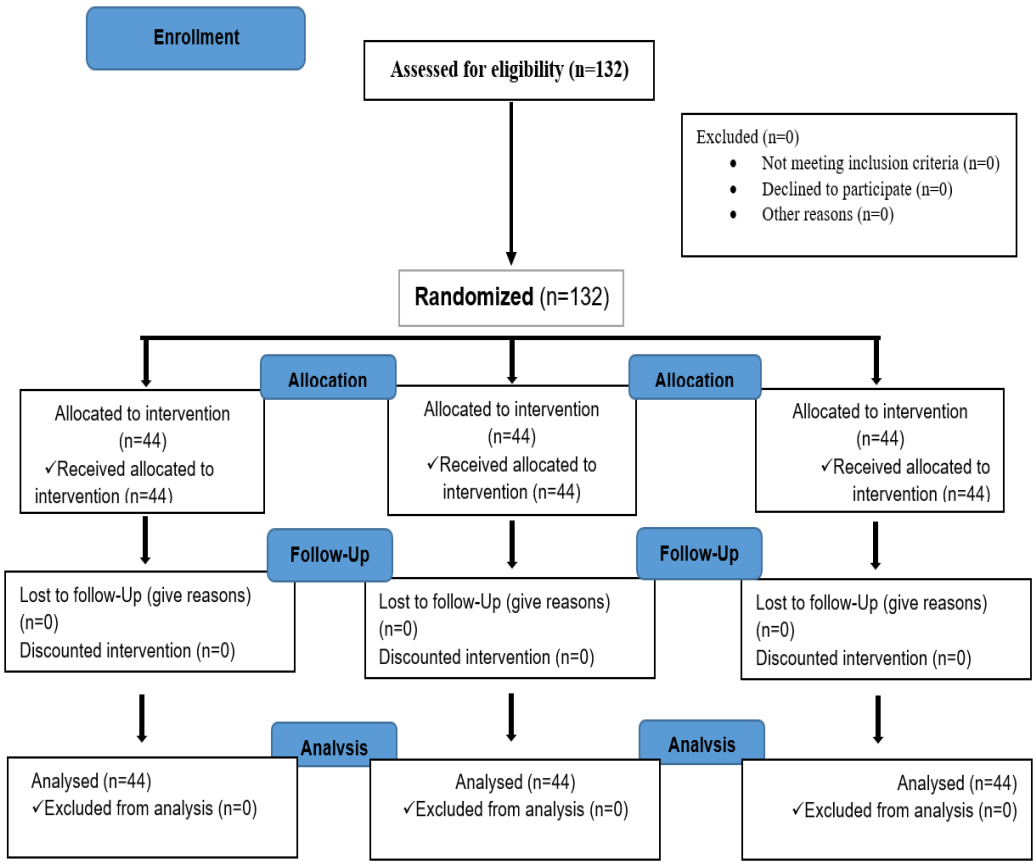
Patients were divided into three groups: pre ECT who received midazolam with the usual regimen before the electric shock, post ECT who received midazolam after the shock, and control group who received routine treatment (without Midazolam), with the same mean age and distribution of gender in three groups.

The drugs were delivered to the anesthesia site in three packages A, B and C, each pack containing 4 syringes so that the injector, the patient and the monitoring provider were not aware of their contents. This was done in order to create blindness of the personal to the study.

The anesthesia regimen given to all three groups consisted of 2 mg/kg sodium thiopental and 0.5 mg/kg succinylcholine with the difference being that group A received 1 mg midazolam before induction and 1 ml normal saline after ending of shock, group B received 1 ml normal saline before induction and 1 mg midazolam after ending of shock but group C received 1 ml of normal saline before induction and after ending of shock.

Patients were kept NPO (non per os) for at least 6 hours, with an IV line taken for them, then a monitoring devices were attached to the patients and Bi-temporal ECT electrodes were placed on the patients' head. After prescribing the drugs, a tooth protector (Mouth Protector) was installed for the patient to prevent the tongue from biting and then the patient was electrically stimulated at 120-90 volts to start the seizure. Patients were then given 100% oxygen until complete recovery. During this treatment, patients were recorded for ECG, blood pressure, oxygen saturation and pulse rate at 5, 10 and 15 minutes after drug injection. Also, the time required to return of complete consciousness and the ability to execute verbal commands was recorded. After becoming fully conscious, patients were asked about headache, nausea, and muscle aches. Samples were selected using easy sampling method and drugs were randomly assigned by simple random sampling. For data analysis, the PASW version 18 software, Predictive analytics software and Chi-square and Independent t tests were used. For repeated data analysis, repeated measures ANOVA was used (Figure 1).

Figure 1- Study flow diagram



Results

Characteristics of the patients

In this study, out of 67 randomized patients, 67 were eligible for the efficacy outcome measures referred to the child and adolescent psychiatry ward, 23 in the midazolam injection pre ECT group, 23 in the midazolam injection post ECT group and 21 subjects were assigned to the control group (Fig 1). Mean age of adolescents in the pre ECT group was 15.4 (±1.9) years, in the post ECT group it was 15.3 (±1.9) years and in the control group it was 14.7(±6) years (Table 1).

One-way analysis of variance showed that the mean age of adolescents was not significantly different between the three groups (P = 0.37). Also there was no significant difference in the frequency distribution of the adolescent's gender between the three groups based on Chi-square test (P = 0.59).

Hemodynamic changes

Vital signs of the patients included systolic blood pressure (SBP), diastolic blood pressure (DBP), moderate blood pressure (MBP), heart rate (PR), and arterial oxygen saturation (SPO2), which were recorded at different times. According to Table 2, the mean systolic and the mean diastolic blood pressure in the first and fifth minutes after the seizure was significantly higher than before the seizure, then decreased in the tenth minute after the seizure and increased again. There was no significant difference between the three groups.

Analysis of variance with repeated variables observations showed that the effect of time on systolic blood pressure was significant (P <0.001) but the effect of group was not significant (P = 0.51). Also, based on the data obtained in Table 2 and analysis of variance test by repeating the observations, it was concluded that the effect of time on diastolic blood pressure was significant (P <0.001) but the effect of group was not significant (P= 0.55).

The difference in mean blood pressure (MAP) at different times in the three groups, based on repeated measures analysis of variance, and the effect of time on MAP was significant (P <0.001) but the effect of group was not significant (P = 0.99).

Mean blood pressure in the first and fifth minutes after seizures was significantly higher than before seizures, then decreased in the tenth minute after seizures and increased again after seizures, and these changes were significantly different between the three groups. The analysis of variance test with repeated observations showed that the effect of time (P <0.001) and also the effect of group (P = 0.02) on heart rate were significant. As the average heart rate increased over time and then decreased. In addition, the mean increase in heart rate over time in the control group was more than the other two groups. In another study based on analysis of variance by repeating the observations (Tables 2, 3), it was shown that the effect of time (P <0.001) and also the effect of group (P = 0.007) on arterial oxygen saturation (SPO2) was significant. So that the average SPO2 decreased over time and then increased. Also, the decrease and increase of mean SPO2 over time in the control group was more than the other two groups (Table 2).

One-way analysis of variance test showed that the mean duration of seizure ending to initiation of verbal response was not significantly different between the three groups (P = 0.30) but the mean duration of induced seizure (P = 0.002), duration of return of spontaneous respiration from cessation of seizures (P <0.001), duration of cessation end to full consciousness (P = 0.005) and duration of recovery stay (P <0.001) between the three groups showed a significant difference.

The mean duration of return of spontaneous respiration from the time of cessation of seizures in group A was significantly less than group B and in group B less than group C (P <0.001). The mean duration of seizure until full consciousness in group A was significantly less than the two groups B (P = 0.03) and C (P = 0.001), but there was no significant difference between groups B and C (14 / 0 P =). The mean length of recovery stay in group A was significantly less than two groups B (P = 0.01) and C (P <0.001) and in group B was less than group C (P = 0.04) (Table 3).

The Chi-square test also showed that the frequency of muscle pain after full consciousness in group C was significantly higher than group B and in group B higher than group A (P <0.001). Chi-square test with likelihood ratio showed that the frequency of headache (P <0.001), coughing (p= 0.04) and nausea (p=0.001) in group C was significantly higher than groups A and B but the occurrence of laryngospasm was not significantly different (p=0.042) (Table 4).

Ultimately, there were no differences between the three treatment groups in the systolic blood pressure (SBP), diastolic blood pressure (DBP), moderate blood pressure (MBP), heart rate (HR) and arterial oxygen saturation (SPO2). Comparison of complications of midazolam between the three groups were reported before and after ECT on headache, muscle pain and nausea and compared with the control group (Table 4), Cough (P = 0.04) and nausea (P=0.001) in the pre-ECT group were significantly higher than the two groups, but the frequency of laryngospasm was not significantly different between the three groups (P=0.42). Laboratory tests showed no clinically meaningful differences.

Table 1- Mean Age and distribution of gender in three groups

Variables	UNIT	Control	Pre ECT	Post ECT	P value*
Age	yrs.	14.7±1.6	15.4±1.9	15.3±1.9	0.37
	F	13-(61.9%)	14-(60.9%)	17-(73.9%)	P value**
Gender					0.59
	M	8-(38.1%)	6-(26.1%)	9-(39.1%)	

*Onaway ANOVA test **Independent t-test

F, Female; M, Male; electroconvulsive therapy.

Table 2- Mean SBP, DBP, MAP, PR and SpO2 in three groups.

Variable	Time	Control		Pre ECT		Post ECT		P value*
		Mean	SD	Mean	SD	Mean	SD	
SBP	BS	125.4	16.9	126.6	11.2	125.1	11.1	
	1st min	138.7	13.6	148.9	25.3	143.5	21.4	
	5th min	160.8	15.6	147.7	15.9	157.4	15.3	0.51
	10th min	131.5	10.7	129.9	11.7	134.4	11.3	
	ES	156.9	11.9	149.6	12.5	161.2	15.7	
DBP	BS	79.9	8.7	78.1	6.8	77.9	8.1	
	1st min	86.3	7.4	89.9	14.8	87.6	14.5	
	5th min	96.5	15.9	90.7	14.4	90.2	8.6	0.55
	10th min	83.2	6.6	80.2	8.5	84.3	7.8	
	ES	90.5	6.2	95.9	15.6	90.8	6.2	
MAP	BS	95.1	9.8	94.3	6.9	93.7	8.2	
	1st min	103.8	7.3	109.6	16.4	106.2	16.4	
	5th min	117.9	14.7	109.7.9	12.9	112.5	10.2	0.99
	10th min	99.3	6.6	96.8	8.2	100.9	8.2	
	ES	112.6	7.4	113.8	13.2	114.2	8.9	
PR	BS	85.5	11.2	84.4	14.1	85.0	15.3	
	1st min	104.8	15.7	105.1	23.9	98.7	15.5	
	5th min	133.6	31.8	124	23.9	118.8	23.9	0.02
	10th min	114.8	15.6	98.7	14.3	108.4	20.6	
	ES	95.6	12.1	86.6	12.2	87.4	14.9	
SpO2	BS	96	0.9	96.8	1.9	96.2	1.5	
	1st min	91.9	2.9	94.2	3.8	91.9	3.2	
	5th min	87.2	3.9	91.4	4.8	90.3	5.5	0.007
	10th min	95.5	1.1	96.8	2.7	96.3	2.1	
	ES	95.8	0.7	96.9	1.3	96.1	1.9	

*Independent t-test

SBP, Systolic Blood Pressure; DBP, Systolic Blood Pressure; MAP, Mean Blood Pressure; PR, Pulse Rate;SpO2, saturation of peripheral oxygen;ECT, Electroconvulsive Therapy; BS, Before Seizure; ES, End of Seizure

Table 3- Determine and compare the average time under study in the two treatment groups

Parameter	UNIT	Control		Pre ECT		Post ECT		P value*
		Mean	SD	Mean	SD	Mean	SD	
Induced seizure	Sec	30.5	4.8	38.3	8.4	32.1	9.4	0.002
From the end of Seizure to the verbal response	Min	12.3	2.6	11.2	5.2	14.4	8.8	0.3
From the end of seizure to back of breathe spontaneously	Sec	83.8	2.6	13.4	6.4	47.4	3.6	<0.001
From the end of seizure to full consciousness	Min	24.9	3.7	19.1	7.3	22.3	5.2	0.005
Recovery duration	Min	43.0	4.9	33.6	6.6	39.1	8.7	<0.001

*Independent t-test

Table 4- Comparison of Complications of anesthesia drugs between three groups

Variables	Control	Pre ECT	Post ECT	P value
	Number -(percentage)	Number - (percentage)	Number - (percentage)	
Headache	9-(42.9%)	3-(13%)	0-(0%)	<0.001
Cough	4-(19%)	2-(8.7%)	0-(0%)	0.04
Laryngospasm	1-(4.8%)	0-(0%)	1-(4.3%)	0.42
nausea and vomiting	8-(38.1%)	2-(8.7%)	0-(0%)	0.001
Muscular pain	15-(71.4%)	1-(4.3%)	5-(21.7%)	<0.001

Discussion

This trial has three important findings. First, midazolam pro-drug plays an effective role in preventing post-ECT complications in children. Second, the drug is safe and third, it can reduce the patient's stress in future visits due to its anterograde amnesia, and this issue is even more so important when the patient is a child. These results are comparable to other studies.

Guidelines recommended sedation for patients undergoing ECT. The ideal sedation should be easy to use and have rapid onset, short duration, and quick recovery [20]. Benzodiazepines have some of these properties, but with some limitations such as prolonged sedation. Midazolam overcame these limitations with a favorable safety profile. It demonstrated a rapid onset and short recovery time. A review of articles on the effects of midazolam as a sedative on complications after ECT showed that premedication is mostly used for reducing pre-anesthesia anxiety in adult patients while reports on its use in pediatric patients with disabilities are difficult to find [22-24].

In a review article in 2017 by Franklin et al. at Vanderbilt University Medical Center in the United States on anesthetics in children undergoing ECT treatment, they concluded that oral or intramuscular prodrugs given to children undergoing ECT, facilitates the separation of the child from the parents and relaxation before venipuncture and has significant effects on the quality of ECT [24]. The results of these studies showed that drugs such as ketamine, clonidine, dexmedetomidine and midazolam are mainly prescribed to provide short but quality sedation during ECT treatment. The decision to induce anesthesia with either of these medications should be based on the child's illness, level of cooperation, the effect of anesthesia on the duration and quality of seizures. According to a study conducted by Seoul University School of Dentistry from 2009 to 2017, induction of anesthesia in adult patients with mental disabilities who refuse to work in the dental office was studied [22].

The present study therefore retrospectively analyzed anesthesia and recovery room records of patients who underwent deep sedation with midazolam. For the purpose of assessing the premedication effect of midazolam, patient cooperation levels during anesthesia induction, administered doses, anesthesia duration, and length of recovery room stay were investigated, and the differences between three groups were analyzed.

Conclusion

In conclusion, using midazolam as premedication in pediatric patients with disabilities and cooperation difficulties can allow anesthesia induction without any physical restraint. The result of this research showed that midazolam prodrug plays an effective role in preventing post-ECT complications in children. The effect of midazolam before and after ECT on headache, muscle pain and nausea was investigated and compared with the control group. Also, due to its forward forgetfulness, midazolam can reduce the patient's stress in the next visits, and this issue is extremely important when the patient is a child.

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