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# The Comparison of Two Anesthesia Induction Methods of Thiopental Sodium - Midazolam and Thiopental Sodium on the ECT in the Major Depression Patients

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**ABSTRACT**

*Major depressive disease is one of the prevalent psychiatry diseases. Its effects on health of patients include desire to commit suicide and resistance to medical treatment. ECT is the most effective method of treatment in this regard. The objective of the study is to compare two anesthesia induction methods of thiopental Sodium and thiopental sodium- midazolam on ECT results in the major depressed patients. The study was conducted as clinical trial research. Sixty major depressed patients needed ECT by approval of psychiatrist were divided into two groups (each containing 30). One group was anaesthetized by thiopental sodium-midazolam, and the other group was anaesthetized by thiopental sodium. The therapeutic response, energy consumed, convulsion duration, and anesthesia and recovery time were evaluated. The independent t-test and Chi-square were used to analyze the data, and SPSS 21 software was used to analyze the output of results. The anesthesia period, recovery time, and Joule given to create convulsion were higher in thiopental sodium- midazolam group (13.70 minutes, 19.73 minutes, 67 Joules, respectively) compared to thiopental sodium group (9.23 minutes, 19.20 minutes, 63 Joules, respectively), but this difference was not statistically significant. The convulsion period in the thiopental sodium (26.03 minutes) group was higher than other group (21.06 minutes), but this difference was not significant (P=0.170). The results show that the reduced dozes of midazolam along with thiopental sodium not only prevent the probability of emergence from anesthesia reactions caused by thiopental sodium, but also leave the minimum effect on convulsion threshold.*

**Keywords**: Depression, Midazolam, Thiopental Sodium, Electroconvulsive Therapy (ECT)

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## INTRODUCTION

Major depressive disease is recurrent disease followed often by severe complications. Electroconvulsive therapy (ECT) in depressed patients who have not responded to medication or have desire to commit suicide and have severe symptoms or intolerance to treatment is a good choice [1]. Major depressive disorder has the highest prevalence among psychiatric disorders during the life (about 17%). Unlike its corresponding drug treatments, electroconvulsive therapy is the most effective treatment for major depression [2]. Electroconvulsive therapy has direct correlation with duration of convulsion [3]. Fast acting treatment is considered as one of life-threatening psychiatric disorders[1] .

Around 70% of patients who do not respond to antidepressant medication might respond positively to electroconvulsive therapy [1]. The effect of electroconvulsive therapy in the treatment of depression has direct correlation with duration of convulsion. Active convulsion caused by electroconvulsive therapy provides optimal antidepressant effect between 25 and 50 seconds [2]. Electroconvulsive therapy has been used for long time by using general anesthesia, including sleeping pills, relaxants, and prescription of oxygen [2]. Ideal anesthetic drug should have fast-acting onset and short duration without opposing effects on the therapeutic effect of convulsion [4]. Barbiturates are drugs causing anesthesia through strengthening or mimicking the Gamma-aminobutyric acid in the brain. The anticonvulsant effects of these drugs are well known. Among this class of drugs, Thiopental Sodium and methohexital are currently used in electroconvulsive therapy [4].

Methohexital is a common drug, but it is less tolerated due to creating pain at the injection site in psychotic patients who are generally mentally fragile. Thiopental Sodium may reduce therapeutic effect of ECT due to strong anticonvulsant effect. Aside from pain at injection site, the use of thiopental sodium in patients treated with tricyclic antidepressants may cause fluctuations in blood pressure and heart rate [5].

Midazolam is a short-acting benzodiazepine, which like other benzodiazepines, acts through effect on GABA1 (which is main inhibitive mediator of brain). Midazolam could be selected as better option since it is secure and safe, it has short-term effect, and it reduces anxiety. Midazolam is prescribed to create relief and neglect before surgery or during induction of anesthesia along with other local anesthetic drugs [6].

Choosing right type of anesthesia drug is one of the methods increasing the therapeutic effect of ECT. In this study, we aim to use combination of Thiopental Sodium and midazolam. Although midazolam (belongs to benzodiazepine category) increases the convulsion threshold and reduces convulsion duration, its reduced doses along with Thiopental Sodium have the minimum effect on convulsion threshold in addition to preventing the risk of emergence from anesthesia caused by Thiopental Sodium. As anesthesia causes considerable anxiety and mental disorder in patients and their companions, reducing anxiety and creating relaxation in them are considered as an essential principle, since it prevents unpleasant mental and emotional consequences. General anesthesia is required in electroconvulsive therapy, but there are fewer studies on the effect of these two drugs. This study examined the anesthesia induction with Midazolam - Thiopental Sodium and Thiopental Sodium during electroconvulsive therapy in patients with depression.

## MATERIALS AND METHODS

This clinical trial study (clinical trial Code: IRCT2016013010741N2) that was a double blind, randomized, and controlled trial was conducted in Kerman Shahid Beheshti Psychiatric Center during 2014-2015. No study has compared two methods anesthesia methods of Midazolam - Thiopental Sodium and Thiopental Sodium in depressed patients so far. Therefore, this study was conducted to fill this gapas it is considered important issue according to experts' view. According to previous similar studies, using different anesthesia drugs, considering the maximum sample size and standard of deviation, and using sample size formula comparing two means, 60 patients who were suffering from major depression confirmed already by psychiatrist and required electroconvulsive therapy were selected by their consent. After Medical Ethics Committee approval (code of ethics: 700/93 / K) and obtaining informed consent from patients, this study was conducted on 60 patients, which all of them were tested by Hamilton Depression Questionnaire (with 17 questions, reliability and validity of 95% and 90% , respectively). Questions of 18-21 are about daily mood changes, but there are not considered in scoring. Out of 17questions, some of them are scored from 0-4, while some others are scored from 0-2. Patients who obtained the score 10-13 were diagnosed as mild depression, patients who obtained score 14-17 were diagnosed as moderate depression, and patients who obtained score over 17 were diagnosed as severe depression. Then, they were divided into two groups (each containing 30 patients) on the day of electroconvulsive therapy based on random numbers of table and two groups were matched in terms of age and gender, and they were assigned randomly into Midazolam + Thiopental Sodium group or Thiopental Sodium group.

The night before electroconvulsive therapy, patients were examined. After entering to electroconvulsive therapy room, patients' vital signs were measured and recorded. Before the induction, 0.01 Mg kg atropine, as anesthesia premedication, was used for all patients.

In the first group, thiopental was injected as much as 3 mg per kilogram for anesthesia and 2.5 mg midazolam along with 5.1 mg kg thiopental were injected in the second group. In both groups, in order to relax the muscles, 5.0 mg

per kg succinylcholine was used. Ventilation and oxygenation in patients were conducted through an appropriate mask with 100% oxygen at 6 liters per minute. After induction of anesthesia and needed readiness, ECT was given by a psychiatrist at standard doses, and onset and end of convulsion were measured and recorded by psychiatrist using ECT automatically.

After two ECT sessions (usually a day after conducting ECT), patients were visited again by the end of the sixth session of ECT by a psychiatrist, and according to Hamilton criterion, depression severity was specified and any complication in each ECT session was recorded.

Electroconvulsive therapy America was initiated by THYMATRON device constructed by USA with 80-Joule energy (in terms of convulsion severity, Joules amount changed according to the anesthesiologist and psychiatrist view). Fasting time was considered 8 hours and patients were preoxigenated 3 minutes before induction of anesthesia. Ventilation of all patients was conducted in controlled way using oxygen 100% by anesthesia bag and mask after anesthesia and before placement of ECT paddles and after removing them until the return of respiration. Electroconvulsive therapy was given after confirming that patient is anesthetized and after muscle fasciculation following administration of succinylcholine.

All patients were monitored in terms of blood pressure and oximetry pulse during anesthesia and after that. Type of anesthesia was selected without informing psychiatrist and one was as responsible for filling out the relevant questionnaire. In all patients, ECT was calculated duration of the convulsion since the brain shock interruption to end of shock movements. In addition, systolic blood pressure, diastolic blood pressure, and pulse of the patient before starting anesthesia at immediately after ECT and 5 and 10 and 15 minutes after the ECT were measured and recorded. In addition, the mean consumption of joules per session of ECT was recorded.

After full return of respiration and stabilization of other vital signs, patients were transferred to the recovery room and they were monitored in terms of occurrence of hallucination. Patients were monitored in the recovery room until cognitive recovery. Duration of anesthesia and recovery time since end of convulsion movement to establishment of vital signs and full patient awaking were recorded.

Exclusion criteria of study included drug allergy, airway obstruction, muscle weakness, liver or kidney disease, a history of drug addiction, severe personality disorder, decreased blood volume, vascular spasm, uncooperative patients due to toxicity, high blood pressure, severe asthma, sever tachycardia (HR more than 100 minutes), obesity, severe sleepiness, all contraindications of electroconvulsive therapy, any experience of consuming alcohol, any drug contraindication during the past three months, unstable medical conditions, hypothyroidism and hyperthyroidism untreated, history of ICH and CVD, accompanied by impaired mental more than major depressive disorder such as dementia, bipolar, pregnancy, external object (Eclipse, electrode intracranial), weight more than 90 kg, taking any medication added outside those prescribed by a psychiatrist, no consent to do ECT, drug abuse, taking psychedelic, untrustworthy family, and lack of consent to continue treatment.

All data of patients were collected through developed questionnaire. Mann-Whitney and Chi-Square test were used to analyze data. SPSS 21 software was also used to analyze output of results. P-values less than 0.05 were also considered as significant.

## RESULTS

Sixty patients were included in this study. They were randomly divided into two groups (each containing 30 people). One group received thiopental sodium- midazolam and the other group was received thiopental sodium. Then, electroconvulsive therapy was performed. The two groups were matched in terms of age and gender (Table 1).

In the two studied groups (thiopental sodium- midazolam and thiopental sodium ), changes of anesthesia duration, recovery time, energy consumed, convulsion time were examined using thiopental sodium- midazolam and thiopental sodium drugs. As you can see in Table 2, the duration of convulsion in thiopental sodium group was higher compared to thiopental sodium-midazolam group, but duration of anesthesia, recovery time, and energy consumption in thiopental sodium-midazolam group were higher compared to thiopental sodium group, and no difference was found between the two groups in these variables ($p>0.05$).

**Table 1- comparing the demographic variables in the two groups**

| | Thiopental Sodium | Midazolam + Thiopental Sodium | p.v |
|---|---|---|---|
| Age (mean ± SD) | 55/03±5/45 | 55±5/53 | 0/981 |
| Gender (Frequency (%)) | | | |
| Female | (60)18 | (63/3)19 | 0/791 |
| Male | (40)12 | (36/7)11 | |

**Table 2- Comparing of duration of convulsion, anesthesia and recovery, and Joules given to patients in the two study groups**

| | Thiopental Sodium | Midazolam + Thiopental Sodium | p.v |
|---|---|---|---|
| Convulsion duration | 26/03±3/03 | 21/06±1/83 | 0/170 |
| Anesthesia duration | 9/23±0/82 | 13/70±1/85 | 0/32 |
| Recovery duration | 19/20±1/21 | 19/73±0/88 | 0/724 |
| Jules given to the patient | 63±2/40 | 67±2/45 | 0/249 |

*Data are shown as mean ±standard deviation based on independent t-test*

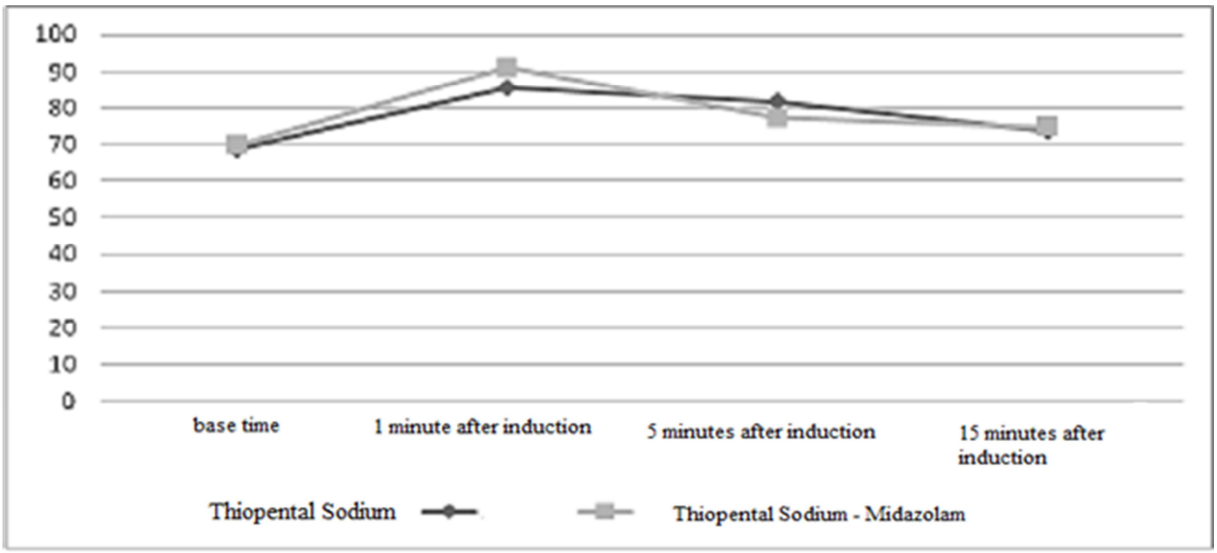


**Chart 1- determining and comparing the arterial blood pressure in two groups at different times**

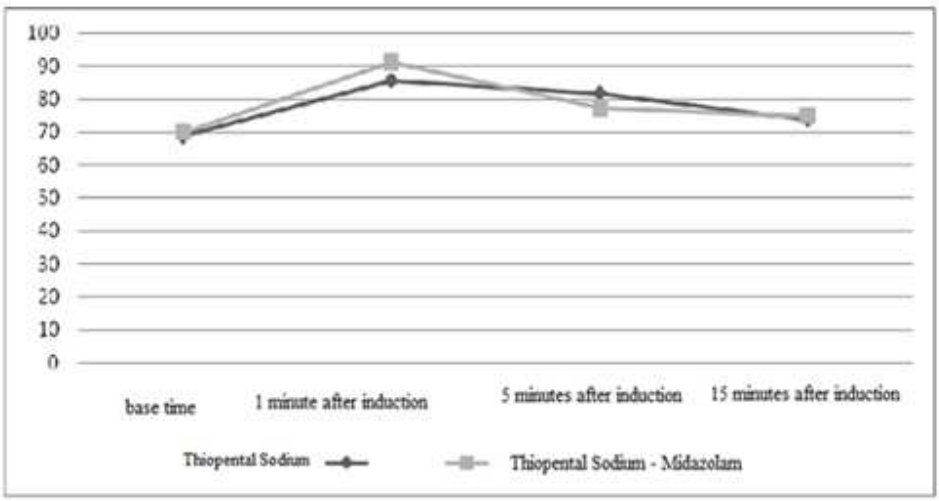


**Chart 2- determining and comparing the heart rate in both groups at different times**

The mean arterial pressure at different times in thiopental sodium group was higher than that in thiopental sodium-midazolam group. However, this difference in the two treatment groups at all times (except for 5 minutes after induction) was not significant (Figure 1). Heart rate at different times after the induction was lower in thiopental sodium-midazolam group compared to thiopental sodium group, but this difference in the two treatment groups at all times (except for 5 minutes after induction) was not significant (Figure 2).

Two groups were also compared in terms of complications. The frequency of bradycardia in thiopental sodium-midazolam group (85.7%) was higher compared to thiopental sodium (14.3%) (P=0.044). Tachycardia frequency and hypertension in thiopental sodium group were higher (52.6% and 60%, respectively) compared to thiopental sodium-midazolam group (47.4% and 40%, respectively), but the difference between two groups was not significant ($p>0.05$).

## DISCUSSION

Severe depression is currently considered as the most important indication for ECT. ECT mechanism of action is not known precisely, but the therapeutic effects of physiological and biochemical changes are created in the central nervous system. In a study conducted by Fink in 1982, he pointed out that the effects of electroconvulsive therapy are caused by Grand Mal convulsion rather than the stimulation of brain cells [7].

Lalla et al showed that convulsion that lasts less than 25 seconds is less effective in terms of treatment [6]. Choosing the right type of anesthetic drug is one of the methods used to increase the effectiveness of electroconvulsive therapy [8]. Methohexital is a common drugs used in anesthesia for ECT, but it is less tolerated in depressed patients who are sensitive and fragile, due to the high prevalence of pain at the injection site. Propofol that is widely used in outpatient practices reduces convulsion time and its application in ECT has been limited. In addition, injection of propofol in narrow blood vessels leads to pain[9].

Finding anesthesia induction drug suitable for restful sleep with minimal effects on blood pressure and rapid heart rate and recovery is one of the most important goals of Anesthesiologists [10]. To avoid emotional and physical trauma during ECT, anesthesia and neuromuscular block are considered essential, and rapid recovery is taken into account in this regard [11]. Thiopental sodium is an intravenous standard drug used in anesthesia, but it is not an ideal option. In this study, we used a combination of thiopental sodium and midazolam. Some researchers believe that midazolam shortens the time of convulsion [12], but its reduced doses along with thiopental sodium leave the minimum effect on convulsion threshold, and it is even recommenced for treatment of agitation after ECT [12].

Age of the patients receiving ECT has increased and this age group of patients is faced with underlying diseases such as hypertension and diabetes and other cardiovascular diseases. On the other hand, they refuse eating and drinking enough due to depression and tachycardia and hypotension are considered as complications of thiopental sodium. Therefore, we decided to use beneficial effects of midazolam, prescribed simultaneously with thiopental sodium, to reduce the side effects of thiopental sodium.

Thus, in this study while recovery time and anesthesia time in thiopental sodium group were lower in comparison to thiopental sodium-midazolam group, the difference was not significant and hemodynamic changes in two groups showed no significant difference at different times. In addition, convulsion time was not different significantly in two groups, while it was higher in thiopental sodium group compared to thiopental sodium-midazolam group. Using thiopental sodium in ECT causes less pain during the injection, but blood pressure and tachycardia increase in thiopental sodium was higher in comparison with thiopental sodium-midazolam group

As general anesthesia is required in electroconvulsive therapy, and there is no study to examine the effect of these two drugs, we examined anesthesia induction using thiopental sodium and thiopental sodium-midazolam. In most of studies, sodium thiopental drug has been measured by other anesthesia drugs for ECT. Results of some of these studies are discussed later.

In a study conducted by Harti et al (2001), 40 cases of ECT in two groups (each containing 20) underwent general anesthesia at a dose of 2-3 mg per kg of sodium thiopental and 1-1.5 mg per kg propofol. According to their study, sodium thiopental is recommended due to easy injection and a lower prevalence of side effects, short acting, inexpensiveness, and good awakening [13].

Result of a study conducted by Alreza et al showed that propofol creates no significant reduction in recovery time and convulsion of ECT patients compared to sodium thiopental, while propofol is more effective compared to sodium thiopental in terms of reducing the hemodynamic response (increased blood pressure) after ECT [14].

In a study conducted by Zeinali et al, it was found hallucination incidence in ketamineis not higher than sodium thiopental, while ketamine in some cases may cause emergence from anesthesia reactions in the form of illusion [15].

## CONCLUSION

Choosing the right type of anesthesia is a method increasing the therapeutic effect of ECT. According to results of this study, we can conclude that reduced doses of midazolam along with sodium thiopental not only prevent emergence from anesthesia reactions caused by sodium thiopental, but also leave the minimum effect on convulsion threshold.

On the other hand, heart rate and blood pressure were lower in the midazolam. Therefore, patients who are older and have comorbidities risk, combination of sodium thiopental-Midazolam is recommended and it is a good alternative to sodium thiosulfate alone.

This study was performed at a mean age of approximately 55 years. After using the combination of sodium thiopental-Midazolam inpatients over 65 years who did included in this study, it was found that changes in blood pressure, heart rate, and agitation after surgery were lower. Therefore, combination of sodium thiopental-Midazolam is recommended in older people.

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