Electroconvulsive Therapy–Related Cognitive Impairment and Choice of Anesthesia

The Tipping Point

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Introduction: Electroconvulsive therapy (ECT) is among the most effective treatments of several life-threatening psychiatric disorder. Despite effective therapy, ECT-induced seizure could cause several adverse effects including cognitive disorders and memory impairment. Drugs such as thiopental, which have been prescribed for anesthesia required for ECT, are known as drugs with cognitive effects. This pilot randomized clinical trial tried to assess the feasibility of using a lower dose of thiopental in combination with remifentanil instead of a higher challenging dose of a single drug with cognitive side effects such as thiopental. We evaluated post-ECT cognitive impairment in patients who received remifentanil-thiopental compared with thiopental-placebo group.

Patients and Methods: One hundred twenty patients with psychiatric disorders between the ages of 18 and 60 years were enrolled. The patients were randomized into 2 groups who received either thiopental sodium (4 mg/kg) and remifentanil (1 μg/kg) or thiopental sodium (3 mg/kg, placebo). The psychiatric patients were examined using mini-mental state examination in terms of the cognitive deficits before ECT as well as 5 and 24 hours after ECT. Statistical analyses were done using Statistical Package for the Social Sciences version 16. Unpaired *t* test, χ^2 test, and analysis of variance were used to determine the association of variables.

Results: All the patients completed the trial. There were no reports of adverse effects. In terms of depth of anesthesia measured by bispectral index, no significant difference was observed. Regarding mini-mental state examination scores, the difference was not statistically significant.

Conclusions: Depth of anesthesia was similar between the groups.

Key Words: electroconvulsive therapy, MMSE, remifentanil, thiopental sodium

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Electroconvulsive therapy (ECT) is among the most effective treatments of several life-threatening psychiatric disorders. Seizures induced by ECT can result in the impairment of cognitive and memory functioning, and the effect of it on brain physiology remains controversial. Retrograde amnesia (inability to remember previously learned information) and anterograde amnesia (inability to retain new information) are 2 types of memory impairment (amnestic disorder) occurring as a complication of ECT.[1]

Such cognitive adverse effects, measured by valid bedside tools such as mini-mental state examination (MMSE), may interrupt further treatment and delay the patient's discharge from the medical facility.[2]

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Common drugs used for anesthesia during ECT are propofol, thiopental sodium, and methohexital,[3–5] and we know the choice of drug plays a role in any resulting cognitive disorder. Propofol, for example, may interfere with the therapeutic effects of ECT owing to the anticonvulsant properties of the drug, and the use of it in some ECT centers has been limited.[6] Various studies have compared the effect of propofol and thiopental sodium on post-ECT cognitive adverse effects, but they all failed to find any significant difference. It has also been shown that remifentanil, when added to propofol, reduces the cognitive impairment after ECT.[5,7,8]

Our pilot study aimed to assess the feasibility of adding remifentanil as an ultrashort-acting opioid to thiopental to use lower doses of anesthetic drug and to evaluate the effect of the new method on cognitive deficits. Considering that our study tested this drug regimen for the first time, we focused on the feasibility and safety of the procedure.

PATIENTS AND METHOD

This study was designed as a pilot double-blind randomized controlled trial (Iranian Registry of Clinical Trials registration number: IRCT201306086280N2) and reviewed by the anesthesia research committee of the Gilan University of Medical Sciences. The study procedures were thoroughly explained to all the patients and their legal guardians, and informed written consent forms were taken.

One hundred twenty patients between the ages of 18 and 60 years with a psychiatric disorder including schizophrenia and mania who were candidates of ECT for the first time were enrolled. Each patient underwent elective ECT procedure at Shafa Hospital of Gilan province in Iran during 2012 to 2013. All patients were thoroughly assessed before undergoing ECT. The exclusion criteria were a history of mental retardation, any severe heart disease, a previous history of ECT, treatment with atypical neuroleptic drugs, American Society of Anesthesiologists class III to IV, uncontrolled hypertension, and any emergency situation including post-ECT agitation needing midazolam. Demographic factors such as age and sex as well as the diagnosis and duration of the psychiatric disorder were recorded. All medications were discontinued throughout the study. The only drug used by all the patients before ECT was reserpine with the recommended dosage of 0.5 to 1 mg/d. The patients were recommended to avoid eating the night before the ECT, and they were allowed to drink until 2 hours before the ECT. The patients were randomized by a software program into 2 groups who received either sodium thiopental-remifentanil or sodium thiopental-saline (placebo). The appropriate dose was calculated for each patient, and considering the compatibility, each patient received the prescribed drugs, either thiopental-remifentanil or thiopental-placebo, in 1 syringe. An anesthesiology resident who was blinded to the prescribed drugs recorded the variable information during the ECT session. A psychiatrist who was blinded to the study groups administered the MMSE. The only person who knew all the details about the study was the executive anesthesiologist who was responsible for the

TABLE 1. Demographic, Clinical, and Treatment Details of Patients Receiving ECT

Parameter	Thiopental-Remifentanil	Thiopental
Age, y	36.9 (9.3)*	35.4 (8.7)*
Sex (M/F)	50/10	40/20
Duration of illness, y	9.2 (7.7)	9.7 (8.4)
Seizure duration, s	23.5 (2.9)	23.2 (2.6)
Amount of energy, %	26.9 (2.6)	27.1 (2.9)
Time of awakening, min	15.8 (5.5)	18.3 (7.04)
Bispectral index (recorded 1 minute after anesthesia)	50.01 (7.99)	50.81 (5.44)

Values are presented as mean (SD).

*$P > 0.05$ when compared with the thiopental group.

F indicates female; M, male.

management of unexpected complications such as hypotension or severe bradycardia. The routine monitoring consisted of electrocardiogram, pulse oximetry, and blood pressure. All the patients received 0.5 mg of intramuscular atropine 30 minutes before the anesthesia. The patients in the sodium thiopental-remifentanil group received 3 mg/kg of sodium thiopental (Chandra Bhagat Pharma Pvt Ltd) and 1 μg/kg of remifentanil (Normon S.A. Pharmaceutical Company, Madrid, Spain); the patients in the control group received 4 mg/kg of sodium thiopental (Chandra Bhagat Pharma Pvt Ltd) and equivalent of isotonic sodium chloride solution as placebo to make the preparations indistinguishable from the drugs used by the anesthesiologist in the other group. Intravascular succinylcholine of 0.5 mg/kg was used for muscle relaxation in both groups. All of drugs were prepared by the executive anesthesiologist to avoid any bias.

Bispectral index monitoring was used to assess the depth of anesthesia. The index of each patients was recorded 1 minute after the infusion of anesthetic drug. Bilateral temporal convulsive therapy was administered by Somatics Thymatron IV equipment using the incremental method to gradually increase the energy setting until the occurrence of a 20-second convulsion. Bispectral index monitoring was used to assess the depth of anesthesia. After the ECT, the patients were transferred to the recovery room to be observed with pulse oximetry, noninvasive blood pressure, and electrocardiogram monitoring. The patients were examined using MMSE to determine any cognitive deficits. The test was performed before the first session of ECT and then 5 hours and 24 hours after the ECT session.

Cognitive disorders were classified according to the following 30-point scoring system: scores of 24 to 30 indicated lack of any cognitive impairment, scores of 18 to 23 indicated moderate cognitive impairment, and scores between 0 and 17 was an indicator of severe cognitive impairment.[1,9]

Statistical analysis was performed using Statistical Package for the Social Sciences version 16. Descriptive statistic tests were used to measure the frequency of variables, and analytic statistic tests including unpaired t test, χ^2 test, and analysis of variance were used to examine associations. The P value less than 0.05 was considered to be significant.

RESULTS

One hundred twenty patients were enrolled in this study. There were 90 men (75%) and 30 women (25%). The mean (SD) age of the patients was 36.2 (9.08) years, ranging from 18 to 60 years. None of the patients were excluded from the study, and no adverse effects have been reported.

The 2 groups were considered identical in terms of age, sex, and duration of psychiatric disorder. Bispectral index value indicated an appropriate level of anesthesia in both groups. Depth of anesthesia measured through bispectral index monitoring showed no significant difference between the 2 groups (Table 1; $P \geq 0.05$). The waking time was significantly less in the thiopental-remifentanil group than in the thiopental-saline group, but the clinical seizure duration was not significantly prolonged (Table 1). Changes in physiologic parameters such as heart rate and blood pressure were also similar in both groups (Table 2). The statistical analysis did not show any significant difference in the MMSE scores between the 2 groups (Table 3; $P \geq 0.05$). Of 60 patients who were given sodium thiopental-remifentanil, 33 patients were without any cognitive impairment and 22 and 5 patients were introduced with moderate and severe cognitive impairment,

TABLE 2. The Hemodynamic Parameter Measured Between the 2 Groups

Parameter	Thiopental-Remifentanil	Thiopental	T value	*P*
MAP (baseline)	86.6 (9.9)	86.07 (9.3)***	0.33	0.74
MAP (post-ECT)	94.07 (14.8)	96.5 (12.9)	0.96	0.33
MAP (recovery)	89.1 (10.2)	86.5 (8.4)	1.53	0.12
HR (baseline)	84.7 (15.6)	84.01 (10.2)	0.28	0.77
HR (post-ECT)	88.5 (14.5)	92.5 (9.8)	1.74	0.08
HR (recovery)	83.5 (12.9)	86.1 (9.2)	1.26	0.20

Values are presented as mean (SD).

*$P > 0.05$ when compared with the thiopental group.

HR indicates heart rate; MAP, mean atrial pressure.

TABLE 3. The MMSE Between the 2 Groups

Parameter	Thiopental-Remifentanil	Thiopental	T value	*P*
MMSE (baseline)	22.18±4.9	22.18±5.4	1.05	0.29*
MMSE (5 h)	22.35±5.3	21.11±5.4	1.25	0.21
MMSE (24 h)	23.23± 4.8	23±5.2	0.25	0.8

Values are presented as mean (SD).

*$P > 0.05$ when compared with the thiopental group.

respectively. There was no statistically significant difference when compared with the other group ($P = 0.18$). Five hours after the ECT in the sodium thiopental-remifentanil group, 25, 28, and 7 patients reported as having no, moderate, and severe cognitive impairment, respectively. After 24 hours of ECT, there were 33, 21, and 6 patients detected as having no, moderate, and severe cognitive impairment. Compared with the other group (sodium thiopental-saline) after 5 and 24 hours of ECT, the statistical analysis showed no significance ($P = 0.14$ and $P = 0.66$, respectively; Table 4).

DISCUSSION

This study showed that adding an opioid such as remifentanil to the anesthetic drug, thiopental, did not have any effects on post-ECT cognitive impairment. Adding the remifentanil at the cost of decreasing the dose of thiopental induced and maintained the required hypnosis. No cases of intraoperative awakening were reported, and there was no need for dose adjustment. Although the depth of anesthesia was the same for both groups, emergence times were not the similar. The remifentanil-thiopental group showed a shorter time to awakening, but it was not statistically significant in comparison with the other group.

In a study conducted by Sullivan and colleagues, 20 patients underwent 38 sessions of ECT using Methohexital or Remifentanil to induce anesthesia. The study showed that the duration of seizure in patients was significantly longer when receiving Remifentanil versus Methohexital; however the recovery time for both groups was similar.[10]

In the study done by Ahsan et al,[7] 20 patients who were treated with ECT twice a week received propofol-remifentanil or propofol-saline for the induction of anesthesia. They reported no significant difference between the 2 groups in terms of recovery time.

Chen[11] reviewed 12 original studies that tried remifentanil for anesthesia in patients receiving ECT. His review supported the use of remifentanil in ECT, particularly in patients with brief seizures, high seizure thresholds, and postictal hemodynamic instability.

Opioids interact synergistically and markedly reduce the dose of sedative-hypnotics required for loss of consciousness and during noxious stimulation.[12]

Ingram and Schweitzer[13] conducted a study to compare the use of propofol with thiopental in 30 patients with major depression in whom ECT was indicated.

Assessment of cognitive impairment was performed at the time of admission, after 6 sessions of treatments, 1 to 3 days after the final treatment, and 1 month after the final treatment. When compared with propofol, thiopental showed less post-ECT cognitive impairment.

Butterfield and Graft[3] performed a randomized, double-blind trial of 15 patients receiving ECT for depression.

Propofol and thiopental were used to induce the anesthesia. Immediate and delayed verbal memory, speed of reaction, and speed of ocular reaction were assessed 45 minutes after ECT. Their results indicated that, with the use of thiopental, the initial recovery period was decreased, whereas the cognitive impairment was increased, suggesting an association of drug with cognitive impairment. They recommended that the drug should be further assessed.

Rezaei et al[8] compared the use of atropine-remifentanil versus atropine-saline (control) premedication protocol in 38 patients with depression who were ECT candidates. Propofol and succinylcholine were used for anesthesia. This study reported less cognitive impairment in the atropine-remifentanil group than in the atropine-saline (control) group, but in our own study, we found no significant differences between the 2 groups regarding MMSE scores($P \geq 0.05$).

In our study, the recovery time of the thiopental-remifentanil group was significantly shorter than that of the thiopental-saline (control) group ($P \leq 0.05$), which may be caused by the lower dose of thiopental (3 mg/kg versus 4 mg/kg) or adding the remifentanil. In the study group, however, no significant differences

TABLE 4. Cognitive Impairment Before and After ECT (Based on the Time of Evaluation)

Parameters	Thiopental-Remifentanil	Thiopental	*P*
Without cognitive impairment before ECT	33 (55)	30 (50)	0.18*
Moderate cognitive impairment before ECT	22 (36.7)	18 (30)	
Severe cognitive impairment before ECT	5 (8.3)	12 (20)	
Without cognitive impairment 5 h after ECT	25 (41.7)	24 (40)	0.14
Moderate cognitive impairment 5 h after ECT	28 (46.7)	21 (35)	
Severe cognitive impairment 5 h after ECT	7 (11.7)	15 (25)	
Without cognitive impairment 24 h after ECT	33 (55)	33 (55)	0.66
Moderate cognitive impairment 24 h after ECT	21 (35)	18 (30)	
Severe cognitive impairment 24 h after ECT	6 (10)	9 (15)	

Values are presented as n (%).

*$P > 0.05$ when compared with the thiopental group, n = 60.

were found between the 2 groups regarding clinical seizure duration or hemodynamic changes ($P \geq 0.05$). It should be noted that the depth of anesthesia measured by bispectral index monitoring was similar in both groups.[12] Cognitive disorder is one of the major complications of ECT, and early cognitive impairment may reduce the cooperation of patient to continue the therapy. General anesthesia, including the common hypnotic drugs of propofol, thiopental sodium, and methohexital, can influence the cognition during ECT treatment.

Thiopental as an anesthetic drug could also have a negative effect on electrical dose required to induce seizures in ECT. Adding remifentanil to thiopental sodium has demonstrated some beneficial effect. Its "sparing effect" could attenuate the dose of the hypnotic drug; this might affect the cognitive impairment after ECT, thus resulting in a shorter recovery time and an early discharge. There are, however, few studies to support this idea.

This pilot control trial was performed on 120 patients with psychiatric disorders using an appropriate sample size, considering randomization and double-blinded processing. Evaluating cognitive impairment after only 1 session of ECT is an important limitation to our study.

Further research is warranted to determine the effect of remifentanil-thiopental on cognitive status after ECT, and if the results turned out to be promising, more trials are recommended to discover the relation of remifentanil to cognitive status, whether it is caused by properties of remifentanil or the sparing effect of it.

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