EFFECT OF REMIFENTANIL ON SEIZURE DURATION AND ACUTE HEMODYNAMIC RESPONSES DURING ELECTROCONVULSIVE THERAPY

REMİFENTANİLİN ELEKTROKONVULSİF TEDAVİDE NÖBET SÜRESİNE VE AKUT HEMODİNAMİK YANITA OLAN ETKİLERİ

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ÖZET

Amaç: Elektrokonvulsif tedavi (EKT) çeşitli psikiyatrik hastalıkların tedavisinde kullanılan bir tedavi yöntemidir. EKT esnasında elektrik uyarısını takiben akut hiperdinamik bir yanıt oluşur.Çalışmamızda remifentanilin oluşan nöbet esnasında görülen geçici hiperdinamik yanıtın kontrolünde kullanılabileceğini öngörmekteyiz.

Metod: 20 erkek ve 20 kadın hasta randomize şekilde çalışmaya dahil edilmiştir. Toplamda 7 EKT tedavisi alan hastaların sondan bir önceki EKT uygulamasında anestezi indüksyonu propofol (1mg/kg) ile yapılırken (grup1) son EKT uygulaması nda propofol (0.5 mg/kg) ve remifentanil (1μg/kg) kullanılmıştır (grup 2).

Bulgular: Grup 1' de kan basıncı değerleri belirli şekilde yüksek iken grup 2' de daha stabil seyretmiştir($p< 0,01$). Kalp atım hızı grup 1' de grup 2'den belirli şekilde fazladır ($p< 0,01$). Motor nöbet süresi grup 2'de belirgin şekilde uzun saptanmıştır ($p< 0,01$). Anesteziden çıkış parametrelerinden olan basit emirlere uyma zamanı, göz açma zamanı ve spontan solunuma dönüş süresi grup 2' de belirgin şekilde uzamıştır ($p< 0,01$).

Sonuç: Çalışmamız sonucunda remifentanil ve propofolun beraber kullanımının EKT için uygun bir teknik olduğu ortaya konulmuştur. Bu teknik nöbet süresine olumsuz etkisi olan propofolün daha az dozda kullanımına imkan sağlamaktadır. Propofol azaltılmasına rağmen hemodinamik stabilite sağlanabilmiştir. Nöbet süresi kısa olan hastalar için bu seçenek akılda tutulmalıdır.

Anahtar kelimeler: EKT, remifentanil, nöbet süresi

SUMMARY

Aim: Electroconvulsive therapy (ECT) is used asa treatment option for individuals with several psychiatric disorder. ECT is often associated with acute hyperdynamic responses immediately after the electrical stimulus. We hypohesized that remifentanil would attenuate the transient hyperdynamic response to ECT without interfering with the seizure activity

Methods: 20 men and 20 women,total 40 patients who went on ECT enrolled in this prospective, randomized trial, each receiving a total of seven electroconvulsive therapies.The patients with cardiac disseases, nouromuscular disseases, instabil hypertension,uncontroled metabolic diseases were excluded. In group I anesthesia induction was achived with propofol (1mg/kg) for next to last ECT and in group II we used propofol (0.5 mg/kg) and remifentanil (1μg/kg) for the last ECT

Results: Blood presure measurments significantly were higer in group I after ECT session while it was more stable in group II ($p< 0,01$).Heart rate was significantly higher in group I than group II ($p< 0,01$). Mean motor seizure duration was found to be significantly longer in patients receiving propofol-remifentanil anesthesia, group II ($p< 0,01$). Recovery parameters were significantly higher in group II which are opening eye time, spontaneus respitarory time and obeying basic command time ($p< 0,01$).

Conclusion: Our results suggest that combination of remifentanil and propofol is useful technique during ECT. This technique allows administration of lover doses of propofol which has fewer effects on seizure duration. A salient point is that heodynamic stability is maintained although the propfol is reduced.This option should be borne in mind when seizure time is shorter than requiredced.

Keywords: ECT, remifentanil, seizure duration.

Table 1. Blood pressure and heart rate values before and after electroconvulsive therapy

	Group I (n=40)		p	Group II (n=40)		p
	Before ECT	**After ECT**		**Before ECT**	**After ECT**	
SAP	125.3±20.2	146.4±33.0	0.001	126.0±21.4	124.9±30.6	0.786
DAP	76.5±11.5	87.5±21.0	0.001	75.8±11.7	75.1±14.5	0.736
MAP	93.1±12.7	108.9±25.4	0.001	93.0±14.0	93.5±17.0	0.856
HRa	86.8±15.9	98.1±18.5	0.001	87.0±16.5	75.3±14.8	0.001

Data are presented as mean±standard deviation.
ECT: Electroconvulsive therapy, SAP: Systolic arterial pressure, DAP: Diastolic arterial pressure, MAP: Mean arterial pressure, HR: Heart rate
aAfter ECT, Group I showed an increase in HR by 13% and Group II showed a decrease in HR by 13%.

Table 2. Duration of seizure and time to regain cognitive functions

	Group I (n=40)	Group II (n=40)	p
Duration of seizure (sec)	30.67±12.96	51.70±28.44	0.001
Time to spontaneous breathing (min)	3.99±1.19	5.66±1.94	0.001
Time to eye opening (min)	6.06±2.16	7.94±2.63	0.001
Time to following orders (min)	7.55±2.56	10.75±3.09	0.001

Data are presented as mean±standard deviation

INTRODUCTION

Electroconvulsive therapy (ECT) is an effective method used for more than half a century for the treatments of major depressive disorder, bipolar disorder and catatonia, which are resistant to medical treatment (1). Although the mechanism of action has not been fully understood, efficacy of ECT depends on the development of generalized seizures (2). Performing the procedure under anesthesia enabled this therapy, which has caused ethical debates, to be considered as a reasonable method. Anesthetic techniques enhanced the comfort and safety of ECT (3).

ECT is a therapeutic method lasting a short time in which rapid changes occur in respiratory, cardiovascular, and locomotor systems, which should be checked simultaneously. Sympathetic activity during ECT leads toacute hyperdynamic cardiogenic effect, which may cause even death.

Use of many different antihypertensive drugs to control the acute hemodynamic responses caused by ECT has gained currency; however, an ideal hypertensive drug, which does not influence seizure duration and efficacy of the procedure during ECT, remains to be defined. Direct-acting vasodilators such as beta-blockers, calcium channel blockers,

2–agonist and antagonists, and nitroglycerin are being used for this purpose (3, 4, 7, 8).

An anesthesiologist is responsible for providing patient's safety and comfort during ECT procedure and for choosing the most appropriate anesthetic agent without making any change in the efficacy of procedure, even by making positive contribution to the efficacy. During ECT procedures performed under general anesthesia, anesthetic agents used are expected to be fast-acting, have painless

injection, cause no hemodynamic effect, show no effect on duration and amplitude of seizure, provide rapid recovery, and be cheap; however, there is no drug covering all these features. Methohexitalis an anesthetic agent, which has been used for long years. Thiopental, propofol, diazepam, ketamine, and etomidate have also been used successfully as induction agents during ECT (3). It is known that remifentanil, one of the opioid agents, reduces the need for primary anesthetic agent. Its hemodynamic stability, rapid action, and short elimination period have enabled remifentanil to be used in ECT procedures as well (9).

The present study aimed to evaluate the effect of remifentanil and propofol combination on motor seizure duration intended to be created during ECT, on the control of acute hypertensive response, and on the duration of recovery from anesthesia.

MATERIAL AND METHOD

In the present study, last two seizures of 40 patients undergoing ECT procedure in the psychiatry clinic were evaluated. Anesthetic agents used in the course of the study were the drugs used in routine ECT anesthesia and no new anesthetic agent was used. The patients and their relatives, and the psychiatrist were informed about the study procedure. Approval of the Ethics Committee of Istanbul University Cerrahpasa Medical Faculty was obtained.

The patients with American Anesthesia Association (ASA) I and II classes and who were medically stable were included. The active ingredients of antipsychotic agents received by the patients were paid attention to be similar. Patients diagnosed with heart disease, having uncontrolled hypertension, endocrinological problems and neuromuscular diseases, using alpha or beta blockers, and receiving antiepileptic medication that was likely to influence duration of seizure were excluded from the study.

Age, gender and body weights of the patients were recorded. In ECT room, electrocardiogram (ECG), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), heart rate (HR), and peripheral oxygen saturation (SpO2) of the patientswere monitored. Intravenous route was opened via 20 G cannula through the dorsum of the right hand or antecubital region to be used during anesthesia induction.

The electrical stimulation applied to the patients during the last two ECT treatments was not changed. Only induction of propofol was carried out in the penultimate ECT (Group I, n=40), whereas remifentanil and propofol combination was used for the induction in the last ECT (Group II, n=40). Thus, same patients were evaluated in two different groups, in which different induction methods were used.

In the Group I, propofol was administered as a slow intravenous infusion in 15 sec at a dose of 1 mg/kg. Inthe Group II,remifentanil was administered as a slow intravenous infusion in 90 sec at a dose 1 μg/kg. Subsequently, propofol was given as a slow intravenous infusion in 15 sec at a dose of 0.5 mg/kg. Loss of consciousness was verified by loss of eyelash reflex in all patients. After providing loss of consciousness, manual ventilation of the patient was provided using 100% oxygen via facial mask by semi-closed, equipped circuit.

Before the use of neuromuscular agent, in order to observe duration of seizure, the right arm was isolated using a tourniquet to prevent succinylcholine passage. After providing loss of eyelash reflex by propofol, succinylcholine was administered at a dose of 1 mg/kg. Duration of seizure was recorded by the nurse, who was working in the ECT unit of the psychiatry clinic and blinded about the anesthetic agent used, considering the time interval that motor movements continued, which was developed after electrical stimulation and observed in the right arm. Cardiac arrhythmias and any non-standard events observed during seizure were also recorded.

After the completion of motor seizure, time to return to spontaneous breathing, time to eye opening, and time to following simple orders were recorded. Time to following simple orders of the patients was recorded considering the orders such as showing their tongues or raising their hands and heads. Moreover, SAP, DAP,MAP, and HR values were recorded 3 minutes after the completion of motor seizure.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS 16. Inc., Chicago, IL, USA). Descriptive statistics were expressed as mean±standard deviation. In the comparison of quantitative data, the parameters were distributed normally; for intergroup comparisons Student t-test was used and for intra-group comparisons paired-samples t-test was used. The results were evaluated within 95% confidence interval at a significance level of $p<0.05$.

RESULT

The mean age of the patients was 39.6□15.7 years (range, 15-82 years) and 50% of them were female. The mean body weight was 72.4±15.9 kg. ASA score was I in 95% and II in 5% of the patients.

There were no significant differences between Group I and Group II in terms of SAP, DAP, MAP, and

HR values before ECT (p=0.885, p=0.774, p=0.987, and p=0.940, respectively). However, SAP, DAP, MAP, and HR valuesafter ECT were significantly lower in the Group II than those in the Group I (p=0.003, p=0.003, p=0.002,and p=0.001, respectively). Blood pressure (SAP, DAP, MAP) and HR values of the groups before and after ECT are demonstrated in Table 1. Intragroup comparisons of blood pressure and HR values before and after ECT revealed that blood pressure and HR values of the Group I were significantly increased after ECT. However, no significant change was detected in the blood pressure values of the Group II; only HR values were significantly decreased after ECT.

The groups were compared in terms of seizure duration and time to regain cognitive functions. Seizure duration, time to return to spontaneous breathing, time to eye opening and time to following simple orders were significantly longer in the Group II as compared to those in the Group I (Table 2).

DISCUSSION

An ideal anesthetic agent that would be used during ECT should be rapidly acting, short-acting, and not reduce the efficacy of treatment provided via epileptic seizure. Most of the short-acting anesthetic agents used during ECT have anticonvulsant effects, and thus decrease the duration and activity of seizure (10). There are studies reporting that the treatment is more efficacious in the event of prolonged duration of seizure created by ECT (11-14). However, there are also studies suggesting that duration of seizure created by ECT has no effect on the clinical outcomes of treatment (15, 16).

Propofolis a hypnotic agent frequently used during ECT. Having rapid action, being rapidly metabolized, not increasing arterial pressure and rarely causing cardiac arrhythmias make propofol to be widely used during ECT. Propofol is rapidly metabolized in a short time after administration of the drug, and is converted into inactive metabolites. Therefore, it has a very short recovery period after anesthesia and causes minimal confusion (17). Moreover, it has also been demonstrated that propofol shortens the duration of seizure by more than 25% during ECT (18). During ECT, propofol can be used in lower doses in combination with remifentanil, which is an opioid agent. Thus, the dose of propofol can be decreased without reducing depth of anesthesia (19).

During the seizure created by ECT, HR and SAP are increased (20). ECT may have fatal consequences particularly in the patients with cardiovascular risks. Owing to the hemodynamic stability provided by remifentanil, it appears as an important agent that can be used by the anesthesiologists to control hemodynamic and cardiac problems caused by ECT (21). Remifentanil is a short-acting narcotic analgesic agent and has been demonstrated to reduce arterial pressure and HR when used during general anesthesia (22).

The present study investigated the effect of remifentanil and propofol combination on the seizure duration, control of hypertensive response, and anesthesia recovery period during ECT procedure. Only propofol was used as the anesthetic agent during the penultimate ECT session (Group I), whereas remifentanil and propofol combination was used in the last ECT session (Group II). The study groups were comparable in terms of seizure characteristics and hemodynamic changes since the same patients were evaluated in both groups.

Recartet al. (23) evaluated 80 ECT administrations of 20 patients. After giving 1 mg/kg methohexital, all patients were randomized into three groups with different remifentanil doses of 25μg, 50 μg,and 100 μg or saline (control), and these four groups were compared in terms of SAP and MAP to investigate their hemodynamic responses. They found no difference between the groups in terms of basal SAP and MAP values. In addition, no differences were found between the groups in terms of durationof seizureactivity, time to eye opening, following orders, and discharge from the recovery room. Change in MAP values before and after ECT was found significantly lower in the group received 100 μg remifentanil as compared to the control group, and they concluded that remifentanil attenuated the hemodynamic response. Nasseriet al. (24) found significant decreases in SAP, DAP, and HR values in the groups received remifentanil during ECT as compared to the control group. The present study also determined significant increases in SAP, DAP, and MAP values after ECT in the Group I. However, in the Group II, no significant changes were found in SAP, DAP, and MAP values both before and after ECT. This suggested that the hemodynamic balance could not have been achieved by propofol alone and that there was an undesired and a hard-to-control increase in arterial pressure after ECT. It was demonstrated that the hemodynamic stability was provided by the use of remifentanil.

Smithet al. (25) compared the group received methohexitalalone with the group received remifentanil and half-dose of methohexitalfor anesthesia induction during ECT and observed that HR was increased in those received remifentanil and half-dose of methohexital. They concluded that this increase

occurred secondary to hypocapnia resulted from the hyperventilation performed before the seizure. In the present study, we avoided hyperventilation and performed normoventilation; thus, controlling the increase in HR could have been provided using remifentanil. Localaet al. (26) found a significant decrease in HR after ECT in the group received remifentanil and low-dose methohexitalas compared to the group received methohexitalalone. Similarly, in the present study, HR was decreased by 13% after ECT in the Group II due to the remifentanil addition to the treatment, whereas it showed an increase by 13% after ECT in the Group I.

In the study by Smith et al. (25),the use of remifentanil in combination with methohexitalprolonged the seizure duration. In another study, Vishneet al. (21) demonstrated that the use of propofol and remifentanil combination significantly prolonged the duration of motor seizure. The present study also found the seizure duration to be significantly longer in the Group II as compared to Group I.

In the study of Akcaboyet al. (27),the duration of motor seizure was found to be significantly longerin the two protocols including propofol in combination with eitherremifentanil or alphentanyl as compared to that in the group received propofol alone.In the same study, time to return to spontaneous breathing, time to eye opening, and time to following simple orders were significantly shorter in the group received propofol alone.

Effects of anesthetic agent used in the patients during ECT on regaining cognitive functions remain to be a conspicuous issue. Current evidences suggest that the use of remifentanil alone or in combination with decreased doses of either propofol or methohexital provides lower seizure thresholds and longer seizure period without making any difference in recovery time(28). Nishikawa et al. (29) recommended the administration of remifentanil in two divided doses. They concluded that using 1 μg/kg and 2 μg/kg of remifentanil in combination with 0.5 mg/kg of propofolprovidedmore satisfactory results in the duration of seizure and hemodynamic stability during ECT as compared to use of onlypropofolat a standard hypnotic dose or 1 μg/kg of remifentanil followed by 0.5 mg/kg of propofol.

The present study found that the time required regaining cognitive functions was significantly longer in the Group II as compared to Group I. Postictal confusion and the use of remifentanil were suggested to be responsible for longer recovery period after the treatment in the Group II. Rezaeiet al. (30) reported that the adding remifentanil to propofol in the patients undergoing ECT did notcause any significant change in the efficacy of ECT and cognitive function, whereas it significantly shortened the reorientation time after ECT. Haas et al. (31) demonstrated that the disease showed the highest clinical regression after ECT in the patient group with seizure duration between 30 and 60 seconds. The worst response to the treatment was observed in the patient group with seizure duration shorter than 15 seconds and longer than 120 seconds. In the present study, the seizure duration of 68 seconds after ECT was recorded in a 21-year-old male patient in the Group I. In the same patient, the time exceeded 120 seconds with the use of remifentanil in combination with propofol and the seizure was stopped with the use of 2 mg bolus of midazolam, which is an intravenous benzodiazepine.

Antipsychotic treatment and level of electrical stimulation have been reported as the factors influencing the seizure duration of the patients (31). In the present study, the electrical stimulation and antipsychotic treatment given to the patients were not changed in the last two ECT sessions. Thus, the increase in the seizure duration of the patients was suggested to be associated with the use of remifentanil and low-dose propofol combination.

The present study aimed to achieve ECT seizure duration with effective and satisfying outcomes by means of remifentanil use. Remifentanil has been suggested to provide prolonged the seizure duration particularly in the patients with short seizure duration (21, 27). However, it should be kept in mind that the use of remifentanil in the patients with longer seizure duration might prolong the seizure duration over 120 seconds, which is accepted to be effective and safe threshold.

It would be unreasonable to expect a painless ECT procedure, in which the patients are treated with electrical shock. In addition to its responsibility to intervene pain in every field and branch of medicine, anesthesiais also responsible for the relief of pain caused by ECT in psychiatric patient. The anesthesiologist should also provide security to the patient against the impacts of ECT on the respiratory, circulatory, and nervous systems.

In conclusion,the present study demonstrated that propofol alone, which is being widely used for ECT anesthesia, failed to provide adequate stability in systemic arterial pressure and HR. This should be particularly taken into account in the presence of heart diseases, in which the hemodynamic stability is considered to be of great importance. Although propofol is known to cause hypotension, it fails to

suppress hyperdynamicresponse occurred due to stress response caused by ECT. The pre**sent study** suggested that hyperdynamic response due to ECT-could be suppressed by adding remifentanil to the treatmentin cardiovascular system. Keeping the seizure duration within the optimum range was also achieved with the use of remifentanil. Considering all these facts, the use of propofol in combination with remifentanil can be considered as an ideal anesthetic technique for ECT.

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