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Original article

Thiopental is better than propofol for electroconvulsive therapy

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Summary. *Background and aim of the work:* electroconvulsive therapy is a psychiatric procedure requiring general anesthesia. The choice of the hypnotic agent is important because the success of the intervention is associated to the occurrence and duration of motor convulsion. However, all available anesthetic agents have anti-convulsant activity. We compared the effect of thiopental and propofol on seizures. *Methods:* We designed a retrospective study at Mood Disorders Unit of a teaching Hospital. Fifty-six consecutive patients undergoing electroconvulsive therapy were enrolled**.** Patients received fentanyl followed by either thiopental or propofol. We evaluated the incidence and the duration of seizure after electric stimulus at the first session of electroconvulsive therapy for each patient. Adverse perioperative effects were recorded. *Results:* Patients were 60±12.1 years old and 64% was female. There was a statistically significant higher number of patients who had motor convulsion activity in the thiopental group when compared to the propofol group (25 vs 13, p=0.023). Seizure duration was statistically significant longer in the thiopental group than in the propofol group (35 sec vs 11 sec, p=0.046). No hemodynamic instability, oxygen desaturation episodes, prolonged recovery time from anesthesia and adverse effects related to anesthesia were recorded. *Conclusions:* Thiopental induction has a favourable effect on seizure when compared to propofol in patients undergoing electroconvulsive therapy. (www.actabiomedica.it)

Key words: electroconvulsive therapy, seizure, propofol, thiopental

Background

Mood disorders are one of the most pressing public health problem worldwide, and the World Health Organization has ranked depression as a leading cause of disability (1-3). The Italian Psychiatrist Cerletti proposed electro convulsion for therapeutic purposes in humans in late 1930s (4). Since then, usefulness and safety of this procedure has been demonstrated in acute schizophrenia, maniac-depressive disorders, and major depression episodes (5). As a consequence, the American Psychiatric Association task force on severe affective illness (DSM IV) considers electroconvulsive therapy (ECT) an effective treatment when pharmacological treatments have failed (6). Electroconvulsive therapy requires general anesthesia with a combination of hypnotic and muscle relaxant drugs (7, 8), and a close cooperation between the anesthesiologist and the psychiatrist is crucial to accomplish an effective and safe ECT (9, 10). The efficacy of ECT relies on the occurrence and duration of seizure after electric stimulus. Unfortunately, currently used hypnotic agents have well-known seizure-suppression activity and may therefore reduce the efficacy of ECT. Different hypnotics were tested (11-17) with methoexitone being the mostly used agent for ECT (18-19), but ac-

tually unavailable outside the United States of America. Among available agents propofol seems to offer a superior hemodynamic stability during the procedure and a quicker recovery time with a lesser alteration on cognitive status (20, 21). However, it might have the disadvantage of reducing the length of seizures when compared to the thiopental (22, 23). Recently, there has been a growing interest in the use of additives (e.g. opioids) associated to induction agents for ECT. An opioid drug can be added to hypnotics for its additive effect on consciousness level and for reducing the dose of hypnotic agents (24-26). Aim of our study was to compare, for the first time, the effects of thiopental and propofol on the occurrence and duration of seizures for the first session of ECT in patients also receiving an opioid.

Methods

This retrospective study was carried out in conformity with the Italian law on privacy (Art. 20–21, DL 196/2003 (http://www.garanteprivacy.it/web/guest/home/docweb/-/docweb-display/docweb/1115480), published in the Official Journal no. 190 of August 14th, 2004) which explicitly exempts, consistently with a European Directive (28, 29), the need of ethical approval for analysis of anonymous data (Preamble #8). We collected the data of 56 consecutive subjects hospitalized at Mood Disorders Unit of San Raffaele Hospital (Milan, Italy) between 2009 and 2015 who underwent ECT for major depression or bipolar disorder, in current severe depressive episode. Inclusion criteria were: patients aged older than 18 years and affected by Treatment Resistant Depression, defined as at least 2 different antidepressant agents used without success (30). Patients with severe aortic valve stenosis, implantable cardiac defibrillators, uncontrolled hypertension, clinically significant respiratory, renal or hepatic disease, abdominal aortic aneurysm, endocrine disorders, neuromuscular diseases, space-occupying brain lesions, and a history of adverse reactions to any anesthetic drug or with a history of alcohol or drug abuse were excluded. Between 2009 and 2012, patients received thiopental as hypnotic agent, while in the period from 2012 to 2015 patients received propofol. Even if all patients underwent multiple sessions of ECT, in this study we considered only the first session of ECT for each patient. A complete clinical evaluation was performed in order to assess diagnosis and treatment. Course of illness was monitored with specific clinical assessment and with Hamilton Depressive Rating Scale (HDRS) weekly. During hospitalization, each patient continued the pharmacological antidepressant treatment with SSRI, SNRI or TCA. Haloperidol (maximum 1 mg/die) was administered in those patients with delusional symptoms. No lithium, anticonvulsants or benzodiazepines were allowed. All patients underwent pre-operative evaluation by an attending anesthesiologist. Non-invasive blood pressure (NIBP), three-lead electrocardiogram and pulse oximetry were monitored during ECT procedure. All drugs were administered intravenously. A tourniquet on the contralateral arm to that used for IV drugs administration was used to exclude the arm from the neuromuscular blocking action and allow the assessment of seizure duration. Before anesthetic induction, patients were pre-oxygenated with 6-8 L/min pure oxygen via a face mask to obtain peripheral oxygen saturation (SpO2) of 98-100%. Anesthesia was induced with fentanyl (0.5-1.0 mcg/kg bolus) followed by a bolus either thiopental (2-2.5 mg/kg) or protocol (1-1.5 mg/kg) over a period of 20 seconds. After loss of consciousness and loss of eyelash reflex, succinylcholine (0.5-1 mg/kg bolus) was administered to achieve muscular paralysis and prevent trauma from seizures. At the end of muscular fasciculation phase, ECT was performed. The electric shock was delivered bitemporally with MECTA Spectrum Device after dental protection had been inserted. The EEG tracing was recorded continuously from two frontal electrodes. Manual ventilation assistance through a face mask with oxygen 100% was ensured during induction and after electric stimulus until the return of spontaneous respiratory activity. Patients were transferred to the recovery room after the achievement of psychomotor recovery. The discharge to the ward was authorized by the attending anesthesiologist once the patient showed an Aldrete score >9. Primary outcome of the study was to evaluate the effects of two different hypnotics (thiopental versus propofol) in combination with fentanyl on the occurrence of seizure in patients undergoing ECT. Second-

ary outcomes included differences between groups in term of duration of seizure in the overall population and in those patients who had motor convulsion activity. We also collected data on hemodynamic instability, oxygen desaturation episodes, prolonged recovery time from anesthesia, adverse effects related to anesthesia, and clinical effectiveness to ECT. The motor convulsion time was defined as the time from the electrical stimulus to the cessation of tonic-clonic motor activity in the isolated hand. Clinical response was defined as reduction of at least 50% of HDRS final score from baseline. Complete remission was defined as HDRS final score was < 8.

Statistical analyses

Sample size was calculated hypothesizing an expected mean±standard deviation seizures duration of 26.4±13 seconds in the thiopental group and of 17.4±6.1 seconds in the propofol group as suggested in previous published studies (30, 31). Considering a significance level of 0.05 (two sided) and power of 90%, we calculated that enrollment of a minimum of 50 patients was needed. Statistical analyses were performed with the use of STATA version 13 (Texas - College station). Continuous variables are presented as mean and standard deviation or median and interquartile range (IQR) as appropriate. Categorical variable are presented as absolute number and percentage. Dichotomous variable were compared by two-tailed X2 test or fisher exact test when appropriate. Continuous variables were compared using the Mann-Whitney U test or using the T Student's test of Student when continuous variables were normally distributed. A p-value ≤0.05 was considered significant.

Results

A total of 56 patients were included in this study. Patients were 60±12.1 years old and 36 (64%) were female with no differences between groups at baseline. Forty-five patients (80.36%) had a diagnosis of Major Depression, while 11 patients (19.64%) had a diagnosis of Bipolar Disorder. As reported in Table 1, each patient had life history of multiple episodes (3.5-4.5). At baseline, HDRS score was >30 with at least 30-40 weeks of continuative and treatment-resistant depressive symptomatology. A total of 31 (55%) patients received thiopental and 25 (45%) patients received propofol. There was no difference in intensity of electric stimulus used at the first session of ECT in all patients (Table 1). Occurrence of seizure was statistically significantly higher in patients who received thiopental compared to those who received propofol (25 patients [81%] versus [vs] 13 [52%], p=0.023). Numbers of ECT sessions was statistically significantly lower for patients who had convulsion when compared to those with no convulsion after ECT (8.5±2.3 vs 6.4±2.8, p=0.0017). Among patients with seizures, the duration was significantly longer in thiopental group compared to propofol group (35 [10-40] s vs 11 [0-37] s, p=0.046). No adverse events were recorded in both groups. Patients showed a good clinical response to ECT procedure. More than 90% of patients from both groups achieved clinical response from depressive symptomatology after ECT treatment, and a total of 27 (48.2)% patients fulfilled criteria for complete remission after the last ECT treatment (Table 1), with no difference between the two groups.

Discussion

In our study, we found that use of thiopental is associated with a significantly higher occurrence and duration of seizures after ECT in patients with major depression. Electroconvulsive therapy is a psychiatric procedure useful for patients with depression unresponsive to other pharmacological treatment and its clinical efficacy is related to the occurrence and the duration of seizure after electric stimulus (32, 33). Since most short-acting anesthetics have anticonvulsant effects, they can increase seizure threshold and inhibit spread of the seizure, thus modifying the seizure activity and shortening its duration, potentially reducing efficacy of ECT. Propofol and thiopental are widely used in ECT anesthesia because of their characteristics (such as rapid emergence from anesthesia, minimal postoperative confusion and a lower incidence of hypertension or tachycardia during induction of anesthesia). Anesthetic agents influence seizure duration to

Table 1. Baseline characteristics of included patients, ECT protocol and outcome. Data are presented as number (%), mean±standard deviation or median (interquartile range)

	Thiopental group (n=31)	Propofol group (n=25)	*p* value
Baseline			
Age, years	58.7±13.2	60.6±10.9	0.56
Gender			
Male, n (%)	11 (35.5)	9 (36)	0.94
Female, n (%)	20 (64.5)	16 (64)	0.94
No. of episodes	3.6 (2.5)	4.6 (2.3)	0.12
Duration of current episode, weeks	52.8 (35.5)	39.1 (15.5)	0.08
Age at onset	42.7 (16.8)	37.1 (10.3)	0.16
HDRS at baseline	31.8 (5.1)	30.9 (5.5)	0.58
First ECT session			
Charge, mC	110.7±12.6	103.2±16.5	0.15
Fentanyl, µg	58±14.9	55±14.0	0.54
Succinylcholine, mg	55±9.4	55±14.2	0.87
Outcome			
Responder*	26 (83.8)	25 (100)	0.13
Remission**	13 (41.9)	14 (56)	0.29

HDRS: Hamilton Depressive Rating Scale; ECT: electroconvulsive therapy;
*HDRS score at endpoint reduced of at least 50 % from basal score; **HDRS <8

Table 2. Incidence and duration of seizure after first ECT session. Data are presented as number (%) or median (interquartile range)

	Thiopental group (n=31)	Propofol group (n=25)	*p* value
Seizure occurence, n (%)	25 (80.6)	13 (52)	0.023
Seizure duration, s	35 (10-40)	11 (0-37)	0.046

ECT: electroconvulsive therapy

different degrees. Our study suggests that thiopental is more effective than propofol for anesthesia induction in patients receiving fentanyl since it is associated to a lower number of missed seizure at the first session of ECT (with comparable electric charge). Of note, a missed seizure after ECT is considered a failed session. Interestingly, we also found that patients with a motor convulsion activity at the first session of ECT received a lower total number of ECT sessions, although without a statistically significant difference. Furthermore in the present study we found a statistically significant difference in the duration of seizure following thiopental versus propofol administration, with thiopental use associated with a longer duration. However, it remains unclear whether the effect of propofol in reducing seizure duration compared with thiopental is clinically relevant. An ideal study investigating the effects of intravenous anesthetics would need to show that the decline in depression scores is faster and/or that participants require fewer treatments to achieve a preset goal without altering any co-variants (e.g. energy or electrode placement). Many studies compared different hypnotic agents for anesthesia induction for ECT. A recent meta-analysis reported the results of different trials comparing the use of anesthetic agents (propofol, thiopental, etomidate and methohexital) during ECT procedure (34). The authors found that duration of motor seizures was longer when thiopental was compared with propofol. Patients receiving thiopental recovered more slowly than those who received propofol. The same meta-analysis, reported that propofol dose ranged between 1 and 2.5 mg/kg with a mean dose of 1.5 mg/kg, while thiopental was

used at 2 to 5 mg/kg with a mean dose of 3-3.5 mg/kg. In our study, we administered a fentanyl bolus two minutes prior to propofol or thiopental. With a fentanyl bolus of 0.5-1.0 mcg/Kg, we use a thiopental dose of 2-2.5 mg/Kg, and a propofol dose of 1-1.5 mg.kg, which are lower than reported in literature. In the past, methoexital was the most used agents for ECT. Swain et al. found longer seizure duration with methoexital compared to propofol and thiopental (12). Safety is another important issue, as electroconvulsive therapy could be associated to severe cardiovascular alterations. Many different anesthesiological strategies were tested to avoid acute changes in heart rate and blood pressure during ECT. Jarineshin et al. observed a superior hemodynamic stability with propofol when compared to thiopental in a prospective, randomized study (35). Yazici et al. found a higher incidence of cardiovascular and respiratory side effects when patients received thiopental compared to propofol (36). Purtuloglu et al found a better therapeutic response when induction was performed with propofol compared to thiopental (37). Rasmussen et al. performed a review of literature and concluded that propofol is superior to hypnotics for its hemodynamic stability and its quick recovery (38). Recently the use of opioids in combination with hypnotics increased. Combining opioids with propofol or other anesthetics produces loss of consciousness with a smaller induction dose and thus could potentially increase seizure duration. Akcaboy ZN et al. evidenced longer seizure duration when using alfentanil or remifentanil in combination with propofol, probably due to a reduction in the anesthetic dosage, but with a prolonged time to recovery (39). Dinwiddie et al. found that propofol-remifentanil anesthesia significantly lengthened seizure duration (25). An important finding of our study is that we found no differences on cardiovascular system variables among the two groups, as reported in other RCTs (40, 41). In our experience, we found that a fentanyl dose of 1-1.5 mcg/kg together with a reduced dose of propofol (1-1.5 mg/kg) or thiopental (2-2.5 mg/kg) provided unconsciousness while maintaining effective seizure length. These findings are consistent with those reported by Nguyen and Andersen (42, 43). To the best of our knowledge, no previous studies investigated the combination of fentanyl plus propofol or thiopental for anesthesia induction for ECT. Our experience suggests that also fentanyl could be advisable in combination with common anesthetics in order to reduce the required hypnotic doses.

Safety and efficacy of ECT is well documented (33). Our results strengthen the role of this technique in the treatment of depression. Response rates of 90% in patients with severe depression, non-responsive to common pharmacological approaches, are impressive, considering that those patients have a severe risk of suicide and high rates of morbidity and mortality. There are lot of studies investigating ECT parameters and outcome. Despite the availability of data from randomized controlled trials (RCTs), no clear consensus was reached on defining the 'ideal' seizure quality that would be most effective. Beside anesthetic agents used, differences in energies, waveforms and electrode placement could also influence the results.

Limitations

The results of this study could be limited for the lack of randomization and for the small number of patients enrolled. In conclusion, according to our results, use of thiopental in combination with fentanyl for anesthesia induction for ECT is more effective than a combination of propofol and fentanyl, without increasing risk of hemodynamic instability or prolonged recovery.

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