Original Article

Adding a Low Dose of Fentanyl to Propofol in Patients Receiving Electroconvulsive Therapy: A Randomized Controlled Trial

Varinee Lekprasert MD[1], Piriya Pisessith MD[1], Pichai Ittasakul MD[2]

[1] Department of Anesthesiology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Thailand

[2] Department of Psychiatry, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Thailand

Objective: To evaluate the effects of low-dose fentanyl combined with a reduced dose of propofol on seizure duration and hemodynamic response during electroconvulsive therapy (ECT).

Materials and Methods: Twenty-two patients with the American Society of Anesthesiologist Physical Status II to III undergoing ECT were enrolled in the present study. One hundred and five bilateral ECT sessions randomized to receive thiopental 2 mg/kg, propofol 1 mg/kg, and fentanyl 0.3 mcg/kg, followed by propofol 0.5 mg/kg. Succinylcholine 0.5 mg/kg was used for muscle paralysis. Seizure duration, awakening time and hemodynamic changes were compared between groups.

Results: One hundred and five bilateral ECT treatments were randomized into thiopental group (n=35), propofol group (n=35), and fentanyl plus propofol group (n=35). The thiopental and fentanyl plus propofol groups had longer EEG and motor seizure durations than the propofol group, but the differences were not statistically significant. There was no difference in stimulus intensity across groups. However, fentanyl plus propofol group had statistically significant prolonged awakening time compare with thiopental group [mean difference 2.71, (95% CI 0.37 to 5.06, p=0.019)] and propofol group (mean difference 2.77, 95% CI 0.42 to 5.12, p=0.016). Only systolic blood pressure in propofol group was significantly lower than thiopental group [mean difference –10.4, (95% CI –19.4 to –1.38, p=0.018)]. There were no significant differences in diastolic blood pressure (df=2, F=2.546, p=0.083), heart rate (df=2, F=0.596, p=0.553), or oxygen saturation across group (df=2, F=2.914, p=0.059).

Conclusion: Using a combination of low-dose fentanyl and low-dose propofol during ECT could be beneficial. Further investigation is needed to establish the optimal dose of propofol and fentanyl.

Keywords: Electroconvulsive therapy; Fentanyl, Hemodynamic response; Propofol; Thiopental; Seizure duration

Received 23 June 2021 | Revised 22 September 2021 | Accepted 23 September 2021

J Med Assoc Thai 2021;104(10):1692-7

Website: http://www.jmatonline.com

Electroconvulsive therapy (ECT) is a procedure indicated for major depressive disorder, bipolar disorder, schizophrenia, and treatment-resistant psychiatric disorder[1]. General anesthesia was introduced to improve safety and prevent serious complications such as cardiovascular instabilities, fracture as, well as transient neurologic deficits, and intracerebral hemorrhages[2,3].

Anesthetics such as thiopental and propofol are commonly used in ECT[4]. In the authors' previous study had discovered that propofol induced less increasing incoming blood pressure than thiopental[5]. Propofol, on the other hand, has anticonvulsive properties that reduce seizure duration. Previous studies showed that the attenuated dosage of propofol combined with the short-acting opioid may lessen the effect on seizure duration and provide acceptable anesthetic depth[6-8].

Fentanyl is a potent opioid agonist which can be used as an adjunct to general anesthesia. Fentanyl is commonly given intravenously in dosage of 0.5 to 1 mcg/kg for minor surgical operations. Fentanyl reduced the anticonvulsant efficacy of propofol in laboratory experiments[9]. The benefits of utilizing fentanyl as an adjunct to an induction agent like propofol include blunting the sympathetic stress response[10,11], minimizing pain due to injection of the anesthetic agent[12], and supplementing sedation to reduce the dose requirement of the induction agent[13].

Correspondence to:

Ittasakul P.

Department of Psychiatry, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

Phone: +66-2-2011235, **Fax**: +66-2-354729

Email: pichai118@gmail.com

How to cite this article:

Lekprasert V, Pisessith P, Ittasakul P. Adding a Low Dose of Fentanyl to Propofol in Patients Receiving Electroconvulsive Therapy: A Randomized Controlled Trial. J Med Assoc Thai 2021;104:1692-7.

doi.org/10.35755/jmedassocthai.2021.10.13120

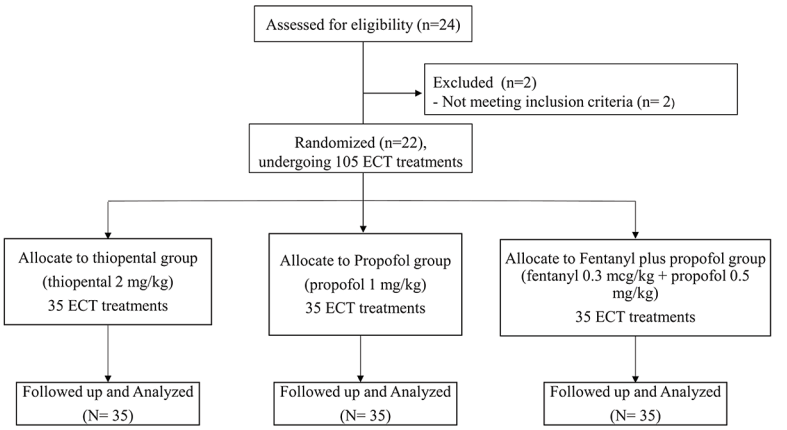

Figure 1. Study flow chart.

The purpose of the present study was to evaluate the effects of adding a low dose of fentanyl to propofol on seizure duration and hemodynamic response during ECT in psychiatric patients.

Materials and methods

Study design

The present study was a randomized controlled trial. The authors randomized ECT treatments of the psychiatric patients to compare seizure duration and hemodynamic response of low-dose fentanyl combined with a reduced dose of propofol versus propofol versus thiopental between September 2015 and August 2017. The study protocol was approved by the Ethics Committee on Human Experimentation of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, approval number: MURA2015/405. Written informed consents were obtained from patients. The present research was conducted in accordance with the Declaration of Helsinki of the World Medical Association[14].

The present trial was registered at the Thai Clinical Trial Registry (http://www.clinicaltrials.in.th) on 27 November 2020, registration number: TCTR20201127005.

Study population and recruitment: The participants were eligible for the present study if they were adults, aged 18 to 65 years old, with the American Society of Anesthesiologist (ASA) physical status I-III, were able to provide informed consent, and scheduled for bilateral ECT treatment at the Department of Psychiatry, Ramathibodi Hospital. Exclusion criteria were patients who had a history of cardiovascular or cerebrovascular disease, poorly controlled hypertension, pregnancy, obesity (body mass index >30 kg/m^2), and had contraindication to use thiopental, propofol, fentanyl, or succinylcholine.

Interventions: Each patient was randomized into three separate groups, 1) thiopental group, receiving thiopental 2 mg/kg, 2) propofol group; receiving propofol 1 mg/kg, and 3) fentanyl plus propofol group, which received fentanyl 0.3 mcg/kg, followed by propofol 0.5 mg/kg. Succinylcholine 0.5 mg/kg was used for muscle paralysis after loss of consciousness (Figure 1).

Randomization: Simple randomization sequence was performed by a statistician with no connection to the present trial, using Stata, version 14 (StataCorp LP, College Station, TX, USA). The randomization sequence list was concealed from the investigators. A nurse anesthetist not participate in the clinical evaluation assigned the participants to their groups The participants were blinded to their treatment assignment.

ECT treatment: Before receiving ECT, all patients were evaluated by psychiatrists and anesthesiologists. Lithium and benzodiazepines were stopped 48 hours and 15 hours before treatment, respectively. ECT procedures were carried out by a team of psychiatrists, psychiatric residents, anesthesiologists, psychiatric nurses, and nurse anesthetists in the post-anesthetic care unit (PACU).

A modified technique involving a brief pulse wave generated by a Mecta Spectrum 5000Q (Mecta Corp, Portland, OR, USA) was applied. The seizure threshold (ST) was determined at the first ECT session using the dose-titration method, as shown in Table 1, except those males started at step 2. The ST was defined as the dose at which there was definite evidence on the electroencephalogram (EEG) of generalized seizure activity for at least 25 seconds.

Table 1. Dose titration schedule and parameter settings

Step	Pulse width (ms)	Frequency (Hz)	Duration (second)	Current (mA)	Charge (mC)
1	1	40	0.75	800	48
2	1	40	1.25	800	80
3	1	40	2	800	128
4	1	60	2	800	192
5	1	60	3	800	288
6	1	60	4.5	800	432
7	1	60	6	800	576

ms=millisecond; Hz=Hertz; mA=milliampere; mC=millicoulomb

None of the patients was administered more than four stimulus doses. The subsequent stimulus intensity was calculated using 1.5×ST[15]. ECT was done three times per week at one- or two-days intervals.

Before induction, the soft bite block was inserted. After proper muscle paralysis, an ECT stimulus was given. This was accomplished by looking for a decrease in deep tendon reflexes and muscle tone. Motor seizure and EEG seizure were monitored using the cuff technique and EEG, respectively.

Throughout the procedures, the airway was maintained and assisted ventilation with 100 percent oxygen was used until the patient restored spontaneous and sufficient breathing. Patients were transferred to the recovery area after the ECT.

Sample size calculation: In the previous studies that measured difference in EEG seizure duration between remifentanil versus propofol, and propofol versus thiopental[5,16], the estimated pooled standard deviation (SD) was 19.19. For sample size calculation and power analysis, the authors used F tests-ANOVA: fixed effects, omnibus, one-way model calculated using G*power software for the difference of EEG seizure duration among groups. (effect size 0.049, type I error 0.05, power 95, dropout rate 10%) 0.05 for type I error, 95 for power, 3 for number of groups and dropout rate 10%. The authors obtained a total sample size of 105 (35 for each arm).

Study outcomes: The primary outcomes were seizure duration measured by motor and EEG activity. The duration of motor and EEG seizure were recorded by a psychiatrist not known the randomization sequences.

The secondary outcomes included awakening time, the change in systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and oxygen saturation (SpO_2) at the endpoint from baseline, were recorded by nurses who did not know the randomization sequences. The awakening time was the time from the ECT stimulus to the patient's ability to open eyes and respond to simple verbal commands and at PACU. The SBP, DBP, HR, SpO_2 were recorded before and after administration of medication, before a seizure, and immediately at the end of the seizure, and at PACU.

Statistical analysis

Data were presented using the mean±SD and percentages for continuous and categorical outcomes, respectively. Data were analyzed by using the IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). The Kruskal-Wallis test was used to determine the non-normality and inhomogeneity of data distribution. Seizure duration (motor and EEG seizure), stimulus intensity, recovery time were compared using one-way ANOVA test among the three groups. Post hoc analyses were performed by Bonferroni post-hoc tests. Interval data (SBP, DBP, HR, SpO_2) were compared by two-way repeated measure ANOVA. A p-value of less than 0.05 was considered statistically significant.

Results

All 105 ECT treatments in 22 patients [9 (40.9%) men and 13(59.1%) women] were analyzed. Seven (31.8%) patients had major depression, 5 (22.7%) had schizophrenia, 5 (22.7%) had bipolar disorder, and 5 (22.7%) had schizoaffective disorder. The mean±SD age of the patients was 42.7±12.88 years (range 27 to 63 years). Eighteen patients (81.8%) were ASA II, and 4 (18.2%) were ASA III. Mean body weight was 71.3±15.3 kg (range 45 to 101 kg).

In terms of seizure duration and recovery time (Table 2), the thiopental and fentanyl plus propofol groups had longer EEG and motor seizure durations than the propofol group, but the differences were not statistically significant. There was no difference in stimulus intensity across the groups. However, fentanyl plus propofol group had statistically significant prolonged awakening time compare with thiopental group (mean difference 2.71, 95% CI 0.37 to 5.06, p=0.019) and propofol group (mean difference 2.77, 95% CI 0.42 to 5.12, p=0.016).

In terms of hemodynamic data, a two-way repeated ANOVA revealed that SBP differed statistically among groups (df=2, F=3.977, p=0.022). SBP in the fentanyl plus propofol group did not differ significantly from the propofol group (mean difference 6.1, 95% CI –2.94 to 15.08, p=0.312) or the thiopental group (mean difference –4.3, 95%

Table 2. Comparison data on seizure duration and recovery time

	Thiopental group; mean±SD	Propofol group; mean±SD	Fentanyl plus propofol group; mean±SD	F	df	p-value
EEG seizure (seconds)	52.3±20.7	46.6±22.1	51.3±22.3	0.696	2	0.501
Motor seizure (seconds)	38.9±16.7	31.6±16.1	39.8±14.7	2.816	2	0.065
Stimulus intensity (joule)	50±37.5	40.4±23.6	41.5±25.7	1.107	2	0.334
Awakening time (minutes)	11.9±3.4	11.9±4.1	14.6±4.8***	5.149	2	0.007

SD=standard deviation; EEG=electroencephalography

* p<0.05 compare with thiopental group, ** p<0.05 compare with propofol group

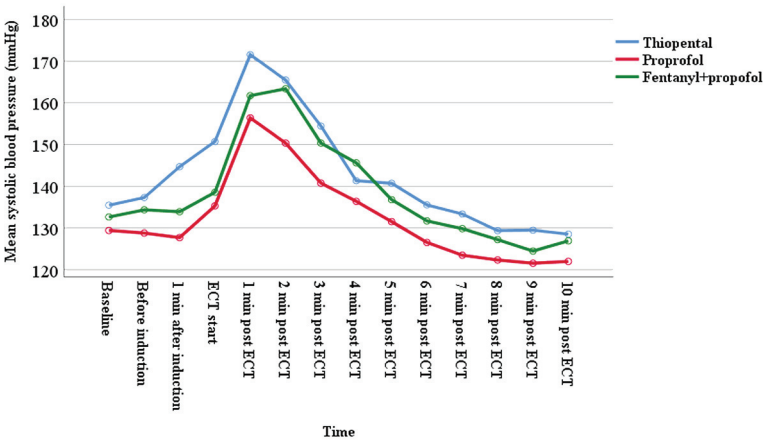

Figure 2. Mean systolic blood pressure (SBP) during ECT.

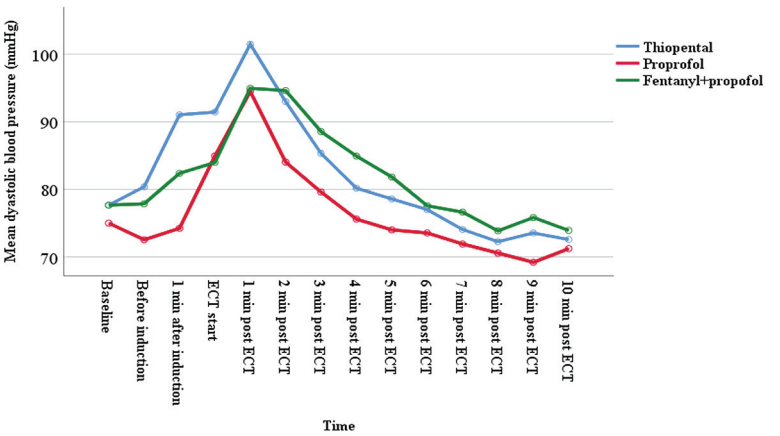

Figure 3. Mean diastolic blood pressure (SBP) during ECT.

CI –13.3 to 4.69, p=0.737) in post-hoc analysis. Only SBP was significantly lower in the propofol group than in the thiopental group (mean difference –10.4, 95% CI –19.4 to –1.38, p=0.018) (Figure 2). Figure 3-5 showed no significant differences in DBP (df=2, F=2.546, p=0.083), heart rate (df=2, F=0.596, p=0.553), or oxygen saturation across group (df=2, F=2.914, p=0.059), respectively.

Discussion

Although there was no statistical significance, the authors discovered that administering fentanyl 0.3 mcg/kg followed by propofol 0.5 mg/kg resulted in longer EEG and motor seizure duration when compared to propofol 1 mg/kg and thiopental 2 mg/kg. In terms of stimulus intensity, there was no differences among groups. Propofol has been demonstrated in

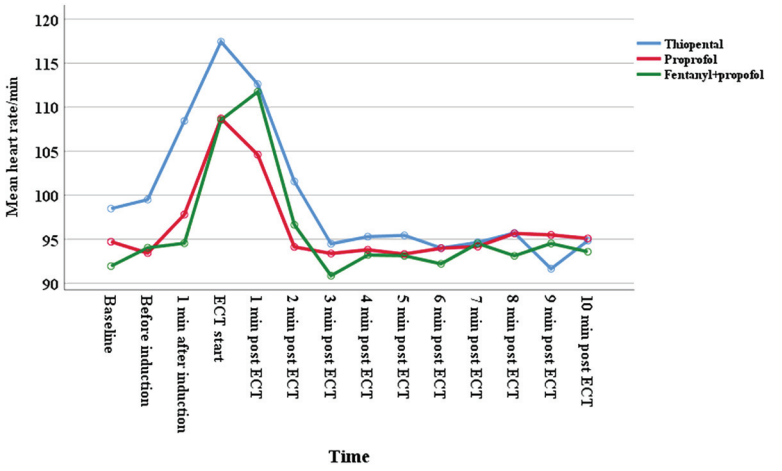

Figure 4. Heart rate/min during ECT.

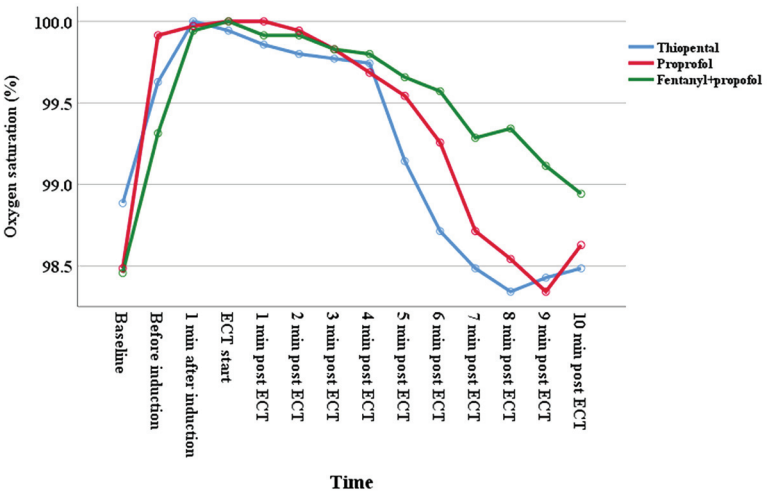

Figure 5. Oxygen saturation (%) during ECT.

previous research to reduce seizure duration[5-8,17]. Low dose fentanyl supplementation provided benefit to reduce propofol dosage, and therefore, to increase seizure duration. However, fentanyl plus propofol group had prolonged awakening time compared to thiopental group and propofol group. This could be explained by the pharmacological combination's synergistic effects.

SBP in the fentanyl plus propofol group did not differ significantly from that in the propofol and thiopental groups. Only SBP in the propofol group was lower than in the thiopental group, however, there were no significant differences in DBP, heart rate, or oxygen saturation among groups. The present study finding was consistent with the previous studies that propofol anesthesia gave more stabilized hemodynamics than thiopental[5,17].

The present study had several limitations. First, subjects included in the present study were all inpatients from a university hospital in Thailand, thus the results should be interpreted with caution in other settings. Second, the sample size was small; type II error may occur. However, the strength of the present study was to explore the effects of low-dose fentanyl combined with a reduced dose of propofol on seizure duration and hemodynamic response.

Conclusion

Using a combination of low-dose fentanyl and low-dose propofol during ECT could be beneficial. It allows administration of a lower dose of propofol but seems to have prolonged awakening time as compared

with others. Therefore, further investigation is needed to establish the optimal dose of propofol and fentanyl.

What is already known on this topic?

Anesthetics such as thiopental and propofol are commonly used in ECT. Propofol induced less increase blood pressure than thiopental. Propofol, on the other hand, has anticonvulsive properties that reduce seizure duration. The attenuated dosage of propofol combined with the short-acting opioid may lessen the effect on seizure duration and provide acceptable anesthetic depth.

What this study adds?

The authors reported the effects of adding low-dose fentanyl to propofol in patients receiving ECT. The result showed adding low dose fentanyl provided benefit to reduce propofol dosage, and therefore increasing seizure duration in patients receiving ECT.

Acknowledgement

The authors would like to thanks Araya Meesomboon, Kritaya Sirirat, and staffs in the Electroconvulsive Therapy Clinic and the PACU, Ramathibodi Hospital, for supporting the data collection process.

Authors' contributions

All authors made substantial contributions to conception and design, acquisition of data, on analyses and interpretation of data, took part in drafting the article or revising it critically for important intellectual content, agreed to submit to the current journal, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Conflicts of interest

The authors have no potential conflicts of interest to disclose.

References

1. American Psychiatric Association. The practice of electroconvulsive therapy: Recommendations for treatment, training, and privileging (A task force report of the American Psychiatric Association). 2nd ed. Washington, DC: American Psychiatric Association Publishing; 2001.
2. Ding Z, White PF. Anesthesia for electroconvulsive therapy. Anesth Analg 2002;94:1351-64.
3. Wells DG, Davies GG. Hemodynamic changes associated with electroconvulsive therapy. Anesth Analg 1987;66:1193-5.
4. Pitidhrammabhorn U, Ittasakul P, Waleeprakhon P, Goldman MB. Clinical characteristics of inpatients undergoing electroconvulsive therapy (ECT) in a university hospital, Thailand. ASEAN J Psychiatry 2016;17:144-50.
5. Lekprasert V, Alunpipatthanachai B, Ittasakul P, Chankam P, Duangngoen P. The Comparison of Hemodynamic Effect of Propofol and Thiopental During Electroconvulsive Therapy: A Prospective Randomized Controlled Trial. J Med Assoc Thai 2020;103:1036-41.
6. Dinwiddie SH, Glick DB, Goldman MB. The effect of propofol-remifentanil anesthesia on selected seizure quality indices in electroconvulsive therapy. Brain Stimul 2012;5:402-7.
7. Nuzzi M, Delmonte D, Barbini B, Pasin L, Sottocorna O, Casiraghi GM, et al. Thiopental is better than propofol for electroconvulsive therapy. Acta Biomed 2018;88:450-6.
8. Sullivan PM, Sinz EH. The use of remifentanil anesthesia for electroconvulsive therapy in patients with high seizure thresholds. J ECT 2004;20:278.
9. Ahmad I, Pleuvry BJ. Interactions between opioid drugs and propofol in laboratory models of seizures. Br J Anaesth 1995;74:311-4.
10. Chung KS, Sinatra RS, Halevy JD, Paige D, Silverman DG. A comparison of fentanyl, esmolol, and their combination for blunting the haemodynamic responses during rapid-sequence induction. Can J Anaesth 1992;39:774-9.
11. Cork RC, Weiss JL, Hameroff SR, Bentley J. Fentanyl preloading for rapid-sequence induction of anesthesia. Anesth Analg 1984;63:60-4.
12. Picard P, Tramèr MR. Prevention of pain on injection with propofol: a quantitative systematic review. Anesth Analg 2000;90:963-9.
13. Sridharan K, Sivaramakrishnan G. Comparison of fentanyl, remifentanil, sufentanil and alfentanil in combination with propofol for general anesthesia: a systematic review and meta-analysis of randomized controlled trials. Curr Clin Pharmacol 2019;14:116-24.
14. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191-4.
15. Ittasakul P, Likitnukul A, Pitidhrammabhorn U, Waleeprakhon P, Goldman MB. Stimulus intensity determined by dose-titration versus age-based methods in electroconvulsive therapy in Thai patients. Neuropsychiatr Dis Treat 2019;15:429-34.
16. Vishne T, Aronov S, Amiaz R, Etchin A, Grunhaus L. Remifentanil supplementation of propofol during electroconvulsive therapy: effect on seizure duration and cardiovascular stability. J ECT 2005;21:235-8.
17. Jarineshin H, Kashani S, Fekrat F, Vatankhah M, Golmirzaei J, Alimolaee E, et al. Seizure duration and hemodynamic state during electroconvulsive therapy: Sodium thiopental versus propofol. Glob J Health Sci 2015;8:126-31.