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ORIGINAL ARTICLE

Ketofol in electroconvulsive therapy anesthesia: two stones for one bird

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Abstract
Purpose Propofol and ketamine have become progressively popular in electroconvulsive therapy (ECT) anesthesia, although propofol shortened seizure duration and ketamine might cause cardiotoxicity, psychotic episodes, and delayed recovery. Ketofol is a combination of ketamine and propofol, and the current study was designed to evaluate the effect of ketamine, propofol, and ketofol on hemodynamic profile, duration of seizure activity, and recovery times in patients undergoing ECT.
Methods Ninety patients (44 women, mean age 27.8 ± 7.2 years) in one ECT session were enrolled and randomized to the propofol, ketamine, or ketofol group. Hemodynamic profile duration of seizure activity and recovery times were recorded.
Results Motor seizure duration in the propofol group was significantly decreased compared to other groups ($p < 0.001$), whereas spontaneous breathing time in the ketamine group statistically increased compared to the propofol group ($p = 0.001$), and also eye-opening time ($p < 0.001$) and obeying-command time ($p < 0.001$) was significantly increased in the ketamine group compared to other groups. Heart rate (HR) at induction (ketamine 91.2 ± 13.6 vs. propofol 77 ± 13.4 and ketofol 79.9 ± 15.6; $p < 0.013$; $p < 0.08$, respectively) was statistically significantly increased in the ketamine group compared to other groups, and HR at the third minute (ketamine 92 ± 12.9 vs. propofol 79.4 ± 9.3 and ketofol 81.5 ± 14.2; $p < 0.012$, $p < 0.048$) was also statistically significantly increased in ketamine group compared to other groups.
Conclusion The ketofol 1:1 mixture is associated with longer mean seizure time than propofol, and shorter mean recovery times than ketamine, with better hemodynamic stability, without any important side effects in ECT anesthesia.

Keywords Ketamine · Propofol · Electroconvulsive therapy

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Introduction

Electroconvulsive therapy (ECT) is an effective procedure for many psychiatric disorders, such as severe depression, bipolar disorder, and schizophrenia [1, 2]. Almost all ECT procedures are performed under general anesthesia with muscle paralysis. The main objective of general anesthesia during ECT is to produce an unconscious state free from recall and muscle paralysis [1], and the choice of anesthetic agent may influence seizure, hemodynamic, and recovery parameters and also cognitive functions after ECT [3]. The ideal anesthetic agent for ECT remains to be established, although several agents including thiopental, methohexital, etomidate, ketamine, propofol, and sevoflurane are used [4].

Propofol has become progressively popular in ECT as it is associated with reasonable hemodynamic response to ECT and quick recovery with little nausea, although it leads to increased seizure threshold and marked shortening of seizure duration [5–7].

Ketamine, an NMDA receptor antagonist, is also a noteworthy anesthetic agent in ECT with favorable seizure-inducing action and increasing seizure duration. Attention has also focused on the possibility of a cognitive function-preserving action by ketamine anesthesia during ECT in recent years [8]. Cardiotoxicity and induction of transitory psychotic episodes, and delayed recovery, are the main drawbacks for ketamine [8, 9].

The combination of ketamine and propofol, referred to by the portmanteau "ketofol," is gaining reputation for various anesthetic procedures [10]. Ketamine mitigates propofol-induced hypotension, and propofol mitigates ketamine-induced vomiting and recovery agitation. The drugs exhibit synergistic and perhaps smoother sedation, and the combination has the theoretical benefits of minimizing the propofol dose and obviating the need for opioid coadministration.

We hypothesized that ketofol would have a favorable effect on seizure duration compared to propofol and would have favorable effects on hemodynamic parameters and recovery times compared to ketamine in contrast to probable additive/synergistic untoward effects of both agents in patients undergoing ECT. Accordingly, the current study was designed to evaluate the effect of ketamine, propofol, and ketofol on hemodynamic profile, duration of seizure activity, and recovery times in patients undergoing ECT.

Materials and methods

Study population

Ninety patients (44 women, mean age 27.8 ± 7.2 years) who were scheduled for ECT treatment for depression (78 patients) and schizophrenia with depression (12 patients) in one ECT session were enrolled, and 90 ECT treatments were evaluated after Institutional Ethics Committee approval and after written informed consent in this prospective, randomized study. The study project was performed in accordance with the most recent version of the Helsinki Declaration. The study population was randomly assigned to receive one of three anesthetic agents (ketamine, propofol, or ketofol).

Exclusion criteria

The exclusion criteria for this study were (1) presence of any serious physical disease, such as cardiovascular disease, cerebrovascular disorder, intracranial hypertension, respiratory tract disease, or severe fracture; (2) hypertension, glaucoma, arterial aneurysm, or cerebrovascular malformation; (3) presence of a foreign body, such as a pacemaker, intracranial electrode, or clips; (4) history of seizures; (5) history of substance abuse or dependence, including alcohol abuse; (6) ASA IV–V status; (7) history of serious adverse effects related to anesthetics, for example, allergy; and a family history of reactions to the study drugs; (8) coexistence of a mental disorder other than major depression, such as dementia and bipolar disorder; and (9) pregnancy.

Anesthesia and ECT administration

Subjects were randomized to propofol group ($n = 30$, 12 women and 18 men), ketamine group ($n = 30$, 16 women and 14 men), and ketofol group ($n = 30$, 16 women and 14 men) with the sealed envelope technique. All chronic antidepressant medication was continued. After premedication with intravenous atropine sulfate (0.25 mg), propofol (10 mg/ml), ketamine (10 mg/ml), or ketofol (ketofol was prepared as a 1:1 mixture of ketamine 10 mg/ml and propofol 10 mg/ml mixed in a 20-ml syringe) was administered slowly (20 mg/10 s) until the patient no longer responded to his/her name being called loudly and showed loss of the eyelash reflex. Additional propofol, ketamine, and ketofol were given in 10-mg increments if the responsiveness to verbal command had not been lost within 60 s after drug administration in each group. The required total dose of propofol, ketamine, or ketofol was recorded. Then, succinylcholine, 1 mg/kg, was administered. Ventilation was assisted with 100 % oxygen in all groups during the procedure. Mean arterial pressure (MAP), heart rate (HR), and oxygen saturation values were recorded at baseline, at induction, and at 1, 3, 5, and 10 min after the end of seizure.

The seizure threshold was determined according to half-age method (% energy = half the age) [11]. A suprathreshold electrical stimulus was given via bifronto-temporal electrodes with a Thymatron System IV, ECT Instrument (Somatics, Lake Bluff, IL, USA). By our observations, the half-age method produced a valid stimulus dose (above seizure threshold). Only one patient failed to seize at the first stimulation with the half-age method on the Thymatron System. The duration of the motor seizure was defined as the time from the ECT stimulus to cessation of tonic–clonic motor activity in the 'isolated' arm. The time from the end of succinylcholine administration until spontaneous breathing, eye opening, and obeying commands was recorded.

Probable side effects, including nausea, vomiting, bradycardia, tachycardia, respiratory depression, hypoxemia, and hypotension/hypertension were recorded immediately before premedication and subsequently at 5-min intervals for up to 20 min after electrical stimulus until the patient was discharged from the recovery unit to the psychiatry department. Respiratory depression was accepted as a

respiratory rate of less than 10 breaths/min, hypoxemia was defined as peripheral oxygen saturation (SpO_2) of 90 % or less, bradycardia was defined as HR less than 50 beats/min, tachycardia was defined as more than 100 beats/min, hypotension was defined as MAP less than 60 mmHg, and hypertension was defined as MAP more than 120 mmHg.

Statistical analyses and sample size

Statistical analysis was performed using SPSS for Windows, version 11.5 (SPSS, Chicago, IL, USA). Distribution of continuous variables was analyzed with the one-sample Kolmogorov–Smirnov test, and all data were distributed normally. Comparisons among groups with respect to seizure duration and recovery parameters were evaluated using one-way analysis of variance (ANOVA) with the Bonferroni post hoc test. Repeated-measures ANOVA with Bonferroni post hoc test was used to compare baseline and follow-up HR and MAP measurements. Side effects among groups were evaluated using the Chi-square test. A two-tailed p value of 0.05 was considered to be statistically significant. The results were expressed as mean ± SD.

Power calculations based on a pilot study with 12 patients to detect a significant difference in the seizure duration ($\alpha = 0.05$, power = 0.80) indicated that 28 patients were needed in each group. We decided to enroll 30 patients in each group.

Results

Motor seizure activity and recovery times after ECT in both groups are shown in Table 1. Motor seizure duration in the propofol group was significantly decreased compared to other groups ($p < 0.001$), whereas spontaneous breathing time in ketamine group statistically increased compared to propofol group ($p = 0.001$); also, eye-opening time ($p < 0.001$) and obeying-command time ($p < 0.001$) were significantly increased in the ketamine group compared to other groups (Table 1). There were no statistically significant differences between groups with respect to side effects (Table 2). Respiratory depression and hypoxemia were not observed among groups. No patient complained about consciousness or memory during anesthesia. Mean total drug dosages for propofol, ketamine, and ketofol groups were, respectively, as follows: 89 ± 10 mg propofol, 84 ± 16 mg ketamine, 43 ± 11 mg propofol, and 43 ± 11 mg ketamine.

MAP measured at baseline, at induction, and at the 1st, 3rd, 5th, and 10th minute after ECT were not statistically significantly different among three groups (ANOVA; $p > 0.05$ for all comparisons) (Fig. 1). Induction MAP values significantly decreased compared to baseline values in the propofol group (73.9 ± 9.9 vs. 70.8 ± 9.7 mmHg; $p = 0.001$). MAP at the 1st, 5th, and 10th minute (75.5 ± 8.0, 74.7 ± 7.7, and 74.5 ± 7.7 mmHg, respectively) in the ketamine group significantly increased compared to baseline values (71.4 ± 9.0 mmHg) ($p = 0.022$, $p = 0.006$, and $p = 0.047$, respectively). MAP did not significantly change during the study in the ketofol group ($p > 0.05$).

Mean HR measured at baseline, at induction, and at the 1st, 3rd, 5th, and 10th minute after ECT are shown in Fig. 2. Induction HR was significantly decreased compared to baseline values in the propofol group (77.0 ± 13.3 vs. 82.7 ± 9.9; $p = 0.032$). In the ketamine group, HR was significantly increased at induction and at the 3rd, 5th, and 10th minute (91.2 ± 13.6, 92.0 ± 12.9, 91.2 ± 12.5, 91.7 ± 13.2, respectively) compared to baseline value (83.2 ± 13.8) ($p < 0.001$, for all comparisons). In the ketofol group, HR did not significantly change during the study. HR at induction (ketamine 91.2 ± 13.6 vs. propofol 77 ± 13.4 and ketofol 79.9 ± 15.6; $p < 0.013$, $p < 0.080$, respectively) was statistically significantly increased in the ketamine group compared to other groups, and HR at the 3rd minute (ketamine 92 ± 12.9 vs. propofol 79.4 ± 9.3 and ketofol 81.5 ± 14.2; $p < 0.012$, $p < 0.048$) was also statistically significantly increased in the ketamine group compared to other groups.

Table 1 Seizure duration and recovery times of patients

Incident	Propofol group ($n = 30$)	Ketamine group ($n = 30$)	Ketofol group ($n = 30$)	p (ANOVA)
Motor seizure (s)	29.3 ± 5.1	37.2 ± 3.2*	34 ± 5.8*	<0.001
Spontaneous breathing (s)	252 ± 13.1	266.6 ± 11.5*	260.7 ± 8.3	0.001
Open eyes (s)	413.1 ± 19.8	538.8 ± 43.2*,+	436.2 ± 32.1	<0.001, <0.001
Obey commands (s)	514.3 ± 38.7	576.5 ± 37.6*,+	519.9 ± 31.1	<0.001, <0.001

* $p < 0.001$ (post hoc Bonferroni) compared with group propofol

+ $p < 0.001$ (post hoc Bonferroni) compared with group ketofol

Table 2 Side effects among groups

Side effect	Propofol group ($n = 30$)	Ketamine group ($n = 30$)	Ketofol group ($n = 30$)	Chi-square, p
Nausea and vomiting (n)	0	2	0	NS
Bradycardia (n)	2	0	0	NS
Tachycardia (n)	2	3	1	NS
Hypotension (n)	1	0	0	NS
Hypertension (n)	0	2	1	NS
Arrhythmia (n)	0	1	0	NS

Side effects among groups were evaluated using the Chi-square test

NS not significant

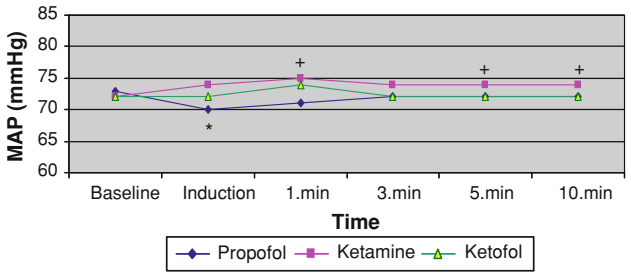

Fig. 1 Mean arterial pressure measured at baseline, at induction, and at 1st, 3rd, 5th, and 10th minutes after electroconvulsive therapy. *MAP* Mean arterial pressure. $^{*}p < 0.05$ versus mean baseline value of group propofol; $^{+}p < 0.05$ versus mean baseline value of group ketamine

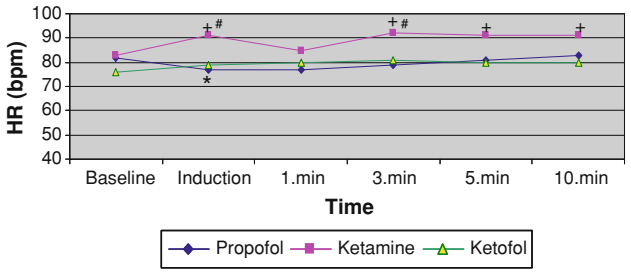

Fig. 2 Mean heart rate at baseline, at induction, and at 1st, 3rd, 5th, and 10th minutes after electroconvulsive therapy. *HR* heart rate, *bpm* beat per minute. $^{*}p < 0.05$ versus mean baseline value of group propofol; $^{+}p < 0.05$ versus mean baseline value of group ketamine; $^{\#}p < 0.05$ compared to propofol and ketofol group

Discussion

With the present study, we have tested the hypothesis that ketofol would have favorable effect(s) on seizure duration compared to propofol and would have favorable effect(s) on hemodynamic parameters and recovery times compared to ketamine in ECT anesthesia. We have shown that (1) both ketamine and ketofol were found to have increased mean seizure duration compared to propofol, (2) ketofol had more favorable hemodynamic effects than ketamine and propofol, and (3) ketamine was found to have longer recovery times compared to both propofol and ketofol.

The combination of propofol and ketamine has been effectively used in separate syringes, as well as mixed in the same syringe, in a variety of settings, including emergency department sedation [12], coronary artery surgery in adults [13], sedation for burns dressings [14], interventional radiology [15], sedation for spinal anesthesia [16], gynecological [17] and ophthalmological procedures [18], and oncologic and orthopedic procedures in pediatric patients [19, 20]. However, there were no studies on the use of ketofol in ECT anesthesia. Ketamine and propofol have also been shown to be physically compatible and chemically stable when mixed in polypropylene syringes and stored at room temperature with exposure to light [21].

Some studies established synergism between ketamine and propofol. Ketamine is known to be an analgesic in subdissociative doses, and when used in combination with propofol, it has been shown to lessen propofol consumption and preserve hemodynamic stability [19]. Aydin Erden et al. [15] have compared the use of a propofol–fentanyl–ketamine combination with a propofol–fentanyl combination as a bolus regimen for interventional radiology procedures. Additional doses of propofol to continue adequate sedation were more often required in the propofol–fentanyl group and desaturation was less frequently observed in the group receiving ketamine as well.

Ketofol has also been studied outside the operating theater setting. When compared to a propofol–fentanyl combination, a combination of propofol–ketamine for deep sedation for burns dressings on the ward was associated with fewer episodes of restlessness requiring further doses of sedatives [14]. The 1:1 mixture was used in titrated bolus doses of 1–3 ml in 114 patients in the emergency department requiring procedural sedation and analgesia, and it was proved to be an effective regimen [12]. Wheatherall and Venclovas [20] showed that ketofol successfully produced deep sedation for prolonged pediatric orthopedic procedures in conjunction with regional analgesia.

The cardiovascular properties of ketamine are well known, and increases in HR and in systolic and diastolic blood pressures are frequently seen during ketamine sedation [22]. In our study, increases in HR and blood pressures compared to baseline levels and compared to

other groups in different time intervals were also observed in the ketamine group.

Agitation and vomiting are adverse effects of ketamine that would be problematic. The incidence of vomiting in adults receiving ketamine is found to be between 5 % and 15 %, whereas the rate of problematic recovery agitation in adults receiving ketamine is estimated to be between 10 % and 20 % [22]. Some studies have reported a low incidence of vomiting and recovery agitation with ketofol compared to ketamine alone [22]. In our study, the incidence of vomiting was also higher in the ketamine group compared to other groups, although the difference was not statistically significant.

As expected, the mean recovery times from ketofol sedation in these series were shorter than those reported in studies of IV ketamine alone and longer than those reported in studies of IV propofol alone [23]. Similarly, we observed significantly increased mean eye-opening and obeying-command times in the ketamine group compared to other groups.

These data suggest that the use of ketamine and propofol in combination might be advantageous for hemodynamic stability and analgesia while decreasing recovery time by reducing the total amount of ketamine. Additionally, it is assumed that the sedative and antiemetic effects of propofol may counterbalance the nauseant and psychomimetic effects of ketamine. Some clinicians favor ketamine and propofol in combination over either agent alone for reasons of this potential balance of effects.

On the other hand, the rationale for combining ketamine and propofol in a fixed ratio would be questioned for reasons of the differing mechanisms of action of the two drugs and the difference in their durations of action [24]. Some authors argued that ketofol is a misleading concept, that it is nothing more than standard propofol sedation in which fentanyl analgesia is replaced with subdissociative ketamine, and they emphasize that there is no compelling evidence that ketofol reduces respiratory depression or produces sedation superior to either ketamine or propofol alone [11]. They argued that it is not logical to administer two drugs and to have to anticipate the unique adverse effects of each when monotherapy works just as well and presents only one set of potential adverse events. They concluded that before ketofol can be recommended, it needs to be established that the combination offers a noticeable advantage over either agent alone [11].

Using ketamine in ECT would have some advantages because of cognitive function-preserving action and antidepressant effect [25, 26]. Okamato et al. [8] showed that Hamilton Depression Rating Scale (HDRS) scores improved earlier in the ketamine group compared to propofol. The authors offered that ketamine may be useful when an early antidepressant effect is needed clinically in severe cases. In another study, Kranaster et al. [27] found that ketamine group needed significantly fewer ECT sessions and had significantly lower HDRS compared to the thiopental group.

Also, there were case reports showing dramatic improvements after the use of ketamine anesthesia in ECT [28, 29]. Ketamine was also found to provide some protection against short-term memory loss, in comparison with etomidate [30]. Possible mechanisms of this favorable effect include suppression of excitotoxicity and neuroprotective action and preventing excessive long-term potentiation induction as an NMDA antagonist [8]. Ketofol, similar to ketamine, would provide cognitive function-preserving effects more than propofol alone with fewer side effects and better recovery times than ketamine alone; attention might be focused on this in further studies.

Several limitations of the present study should be noted. The potential limitations are the absence of evaluating cognitive function-preserving and antidepressant effects of the drugs with long-term follow up and relatively small sample size and the absence of anesthesiologists' and psychiatrists' satisfaction scores. Furthermore, we included 12 schizophrenic patients with depression. Although we did not observe any psychotic symptoms in the ketamine group; using ketamine as an NMDA-receptor agonist in schizophrenic patients might cause schizophrenia-like symptoms and exacerbate psychotic symptoms and cognitive impairment in schizophrenic patients [31, 32]. It should be noted that generalizing data of the present study might not be appropriate because our results denote therapeutic responses of a population from the same geographic region and genetic origin; subjects from other geographic region(s) and genetic origin(s) might respond differently to study medications than did our study population.

In conclusion, the ketofol 1:1 mixture is associated with a longer mean seizure time than propofol, and shorter mean recovery times than ketamine, with better hemodynamic stability without any important side effects in ECT anesthesia. Further studies investigating the optimal doses, cognitive function-preserving effect and antidepressant effects, and physician satisfaction scores should be elucidated.

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