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Premedication with dexmedetomidine and midazolam attenuates agitation after electroconvulsive therapy

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Abstract
Purpose. This study was designed to compare the effects of premedication with dexmedetomidine and midazolam on post-electroconvulsive therapy (ECT) agitation (which patients had experienced previously and had been resistant to treatment). In addition, we aimed to evaluate the duration of convulsion, the propofol requirement, the recovery time, and patients' satisfaction during and after ECT.
Methods. Fifteen patients with depressive episodes of bipolar disorder and nonbipolar recurrent depression and patients who underwent a series of three consecutive ECT treatments were studied as a crossover design. In this double-blind and placebo-controlled study, patients were randomly allocated to receive either dexmedetomidine, 0.5 $\mu g \cdot kg^{-1}$ (group Dex), midazolam, 0.025 $mg \cdot kg^{-1}$ (group Dor), or saline (group C) in a total volume of 20 ml given intravenously 10 min before the induction of anesthesia. Propofol was administered until the patients did not respond to a verbal command.
Results. The mean duration of convulsive activity was longer in group Dex than in group C and group Dor ($P < 0.05$). The total dose of propofol requirement in group Dor and group Dex was lower than that in group C ($P < 0.05$). Agitation scores in both groups Dor and Dex were significantly lower than scores in group C ($P < 0.05$) at 10 and 15 min after ECT.
Conclusion. Premedication with low-dose intravenous dexmedetomidine, 0.5 $\mu g \cdot kg^{-1}$ or midazolam, 0.025 $mg \cdot kg^{-1}$ before ECT may be useful in managing treatment-resistant agitation after ECT, without adverse effects.

Key words Electroconvulsive therapy (ECT) · Agitation · Dexmedetomidine · Midazolam · Convulsive activity

Introduction

Electroconvulsive therapy (ECT) is an effective treatment for a variety of psychiatric illnesses, particularly persistent and severe depression, bipolar disorder, and schizophrenia [1–3]. However, emergence agitation (restless agitation with panic-like behavior, excitement, restlessness, talkativeness, and moaning) [4,5] hyperdynamic response, lessened satisfaction, and seizure activity may occur in some patients after ECT [4–9]. Several treatment modalities have been proposed for post-ECT agitation, such as sedative-anesthetic drugs, midazolam, and antipsychotics. However, these kinds of drugs have an influence on seizure length and they have adverse effects [10–12].

Dexmedetomidine has been studied and reported to be effective in ECT, without serious side effects. Similarly, midazolam has also been studied for ECT. However, the effects of these two sedative drugs have not been compared in agitated patients who underwent ECT. Therefore, in the present study, we aimed to investigate and compare the effects of premedication with a low, single dose of dexmedetomidine and a low, single dose of midazolam in the anesthesia of ECT, and to find the ideal propofol dose to constitute the ideal anesthetic condition for patients who had post-ECT agitation. The present study involved patients who had experienced post-ECT agitation more than once during previous treatments.

It has been stated that dexmedetomidine should be administered over no less than 10 min, as, because of sudden exogenous catecholamine release, the loading dose of up to 1 $\mu g \cdot kg^{-1}$ and too rapid administration can lead to tachycardia, bradycardia, and hypertension [13]. With this in mind, dexmedetomidine, 0.5 $\mu g \cdot kg^{-1}$ was given over 10 min in this study. Fink [14] reported that in moderate to severe cases of agitation after ECT, midazolam (0.5–2 mg) was effective. Therefore, midazolam, 0.025 $mg \cdot kg^{-1}$ was administered to the patients in this study.

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Patients and methods

After the institutional review board's approval of this study, written informed consent was obtained from patients with American Society of Anesthesiologists (ASA) physical status I-II. The work presented was performed in accordance with the most recent version of the Helsinki Declaration.

There were 15 patients in the trial (5 women and 10 men). Twelve patients had had a bipolar depressive episode, and 3 patients had nonbipolar recurrent depression. During three separate sessions, 45 ECT treatments were evaluated in this double-blind and crossover design study, from October 2007 through December 2007. All the patients had had severe post-ECT agitation more than once. The exclusion criteria were: not providing their own consent for ECT, ASA physical status more than II, age less than 18 years, pregnancy, ischemic heart disease, heart blocks, arrhythmia, the use of premedication drugs such as β-adrenergic blockers, the use of tricyclic antidepressant drugs, and a known or a family history of adverse reactions to dexmedetomidine or midazolam.

Patients were assigned to one of three study groups, using a computer-generated random number table. Randomization was carried out confidentially by an anesthetist, and the data were evaluated by a psychiatrist who was blinded to the study. The patients subsequently received an alternative study drug in their next session. The study medication consisted of dexmedetomidine (0.5 $\mu g \cdot kg^{-1}$; Precedex; Abbott, Istanbul, Turkey, 200 $\mu g \cdot 2\ ml^{-1}$), midazolam (0.025 $mg \cdot kg^{-1}$; Dormicum; F. Hoffmann-La Roche, Basel, Switzerland, 5 $mg \cdot 5\ ml^{-1}$), or normal saline in a total volume of 20 ml. The medications were prepared by an anesthesiologist not involved in the measurements and evaluation and were infused intravenously 10 min before the induction of anesthesia. After premedication with the study drugs, propofol was administered slowly (20 $mg \cdot 10\ s^{-1}$) until the patient no longer responded to his/her name being called loudly and showed loss of the eyelash reflex. Then, succinylcholine, 0.5 $mg \cdot kg^{-1}$ was administered. The total dose of propofol the patients required was recorded. Ventilation was assisted with 100% oxygen in all groups during the procedure. After complete neuromuscular blockade and bilateral temporal electrode placement, ECT was commenced with bilateral-bitemporal stimulation. The electrical stimulation was a 120-volt-current for 3 s (EKT03; Gunes Electronic, Gaziantep, Turkey).

The duration of the convulsion was recorded as the time from the ECT stimulus to cessation of tonic-clonic motor activity in the patients' extremities. The isolated cuff technique was not used. The recovery time was recorded as the time from the end of succinylcholine administration until the patients' obeying the commands. Noninvasive mean arterial pressure (MAP), heart rate (HR), oxygen saturation, and probable side effects, including headache, nausea, vomiting, coughing, and fever were recorded immediately before premedication and subsequently at 5-min intervals for up to 15 min after electrical stimulus until the patient was discharged from the recovery unit to the psychiatry department.

Agitation score and the patients' satisfaction were evaluated when the patients were completely awake after ECT. The agitation was evaluated using an emergence agitation (behavior score) score (1 = sleeping, 2 = awake and calm, 3 = irritable and crying, 4 = inconsolable crying, 5 = severe restlessness and disorientation purposelessly wanting to get out of the bed, wanting to stand on the bed, shouting, crying, or mumbling loudly) [15]. Patients' satisfaction was assessed using a satisfaction scale, in which 1 represents pleased and calm, 2 represents the patient is without any complaint and satisfaction is not bad, 3 represents the patient has some complaints and has middling quality of satisfaction, and 4 represents complaints that the treatment is unpleasant, and he/she does not want to undergo the same technique any more.

Respiratory depression was defined as a respiratory rate of less than 10 $breaths \cdot min^{-1}$, hypoxemia was defined as peripheral oxygen saturation (Sp_{O_2}) of 90 % or less, bradycardia was defined as HR less than 50 $beats \cdot min^{-1}$, hypotension was defined as MAP less than 60 mmHg, and hypertension was defined as MAP more than 120 mmHg.

Statistics

Data values are summarized as means ± SD. Parametric data were analyzed and compared using one-way analysis of variance (ANOVA), and multiple measurements were analyzed using repeated-measures analysis of variance. Kruskal Wallis and χ^2 tests were used to analyze for nonparametric data. A P value of 0.05 or less was considered statistically significant.

Results

Forty-five ECT treatments were evaluated in 10 male and 5 female patients (age, 32 ± 9 years; weight, 75 ± 16 kg).

In both the study groups, the agitation score was significantly lower than that in group C at 10 and 15 min after ECT ($P < 0.05$; Fig. 1). After ECT, an additional drug, such as midazolam, 0.025 $mg \cdot kg^{-1}$ or dexmedetomidine, 0.5 $\mu g \cdot kg^{-1}$ for sedation was given to patients who showed agitation grade 4 or 5. Three patients in

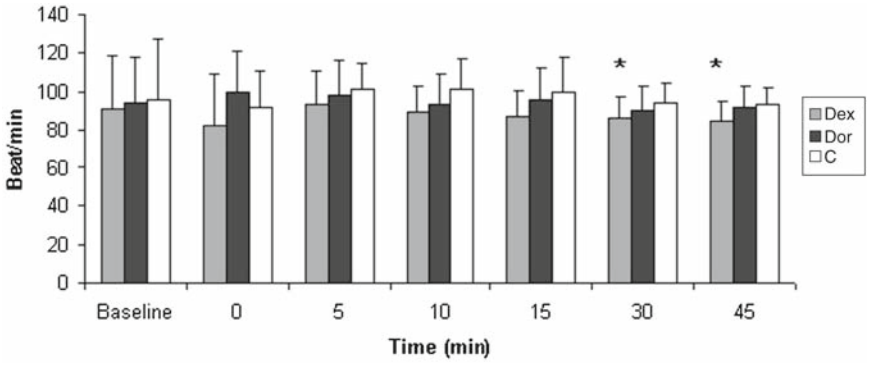

Fig. 1. Agitation scores (means and SD) of the groups ($n = 15$ in each group). The agitation scores in groups *Dex* (dexmedetomidine) and *Dor* (midazolam) were significantly lower than those in group *C* (control) at 10 and 15 min after electroconvulsive therapy (ECT). *$P < 0.05$ compared with group C

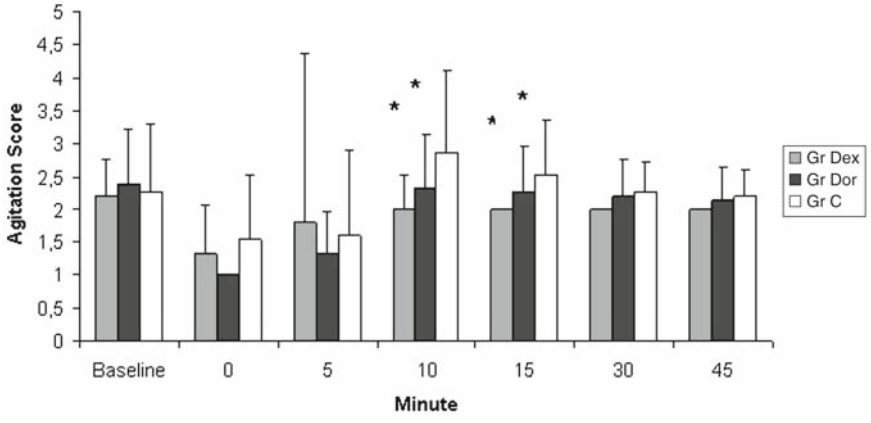

Fig. 2. Mean arterial blood pressure (MAP; means and SD; $n = 15$ in each group). In group Dex, MAP decreased significantly from the baseline value at 30 and 45 min after ECT. *$P < 0.05$ compared with baseline value

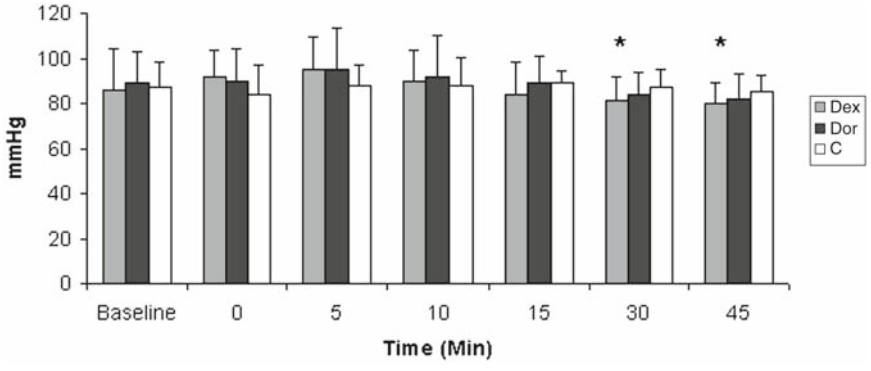

Fig. 3. Heart rate (HR; means and SD; $n = 15$ in each group). HR of the patients in group Dex was significantly lower than the baseline value at 30 and 45 min after ECT (*$P < 0.05$ compared with baseline value)

group C needed supplementary sedation for their intense agitation.

The duration of convulsion was significantly longer in group Dex than in groups Dor and C: Dex > Dor = C (32 ± 13, 23 ± 6, and 22 ± 8 s, respectively, $P < 0.05$; Table 1).

There was no difference among the groups with regard to the recovery time ($P > 0.05$; Table 1).

In group Dex, MAP and HR decreased significantly from the baseline value at 30 and 45 min after ECT ($P < 0.05$; Figs. 2 and 3).

Patients' satisfaction was similar among the groups (Table 1).

The total propofol dose was different among the groups: Dex < Dor < C (56 ± 15 mg, 78 ± 14 mg, and 89 ± 13 mg, respectively; $P < 0.05$; Table 1).

Four patients in group Dex and two patients in group Dor developed coughing. Headache occurred in five patients in group Dex and six patients in group Dor. No patient experienced respiratory depression, hypoxemia, bradycardia, hypotension, or hypertension. None of the patients received atropine or ephedrine.

Table 1. Duration of convulsion, recovery time, satisfaction, and propofol consumption of the patients

Variable	Group C ($n = 15$)	Group Dex ($n = 15$)	Group Dor ($n = 15$)
Duration of convulsion (s)	22 ± 8	32 ± 13*	23 ± 6
Recovery time (min)	8 ± 4	5 ± 2	6 ± 2
Patients' satisfaction (score)	1.80 ± 0.77	1.46 ± 0.51	1.80 ± 0.67
Propofol dose (mg)	89 ± 13	56 ± 15*	78 ± 14**

* $P < 0.05$ (Dex) when compared with group Dor and group C (control); ** $P < 0.05$ (Dor) when compared with control group
Data values are presented as means ± SD

Discussion

Premedication with low-dose intravenous dexmedetomidine, 0.5 $\mu g \cdot kg^{-1}$ or midazolam, 0.025 $mg \cdot kg^{-1}$ before ECT could be useful in managing treatment-resistant agitation after ECT. Both these drugs can reduce the total propofol requirement and lengthen the duration of convulsion during ECT.

There was no significant difference among the groups regarding hemodynamic side effects during ECT. Despite the low doses of propofol in the study groups, hyperdynamic side effects, such as hypertension and tachycardia, may have been suppressed by propofol during the ECT procedure. The decrease in systemic pressure following an induction dose of propofol appears to be due to both vasodilation and myocardial depression. The leading cause may be a reduction in sympathetic activity [16].

The doses of propofol the patients required was different between the three groups in our study (Dex < Dor < C). Dexmedetomidine significantly decreased the total propofol requirement for induction of anesthesia. It also lengthened the duration of convulsive activity during ECT when compared with findings in groups Dor and C, without altering the satisfaction and recovery times of the patients. As dexmedetomidine premedication reduced the total propofol requirement, lower doses of propofol may have affected the tonic-clonic motor activity. Furthermore, the lower doses of propofol may have brought about a shorter recovery time in group Dex, although there was no significant difference in recovery times between the groups.

None of the patients in any of the three groups complained of awareness, according to cross-examination after ECT. No patient in any group remembered any event about the procedure. Therefore, awareness or implicit memory of intraoperative events cannot have affected the patients' satisfaction scores. Postictal amnesia may have been the main reason [17] for this lack of awareness.

The duration of convulsion was significantly longer in group Dex than in groups Dor and C (Dex > Dor = C; 32 ± 13, 23 ± 6, and 22 ± 8 s, respectively). However, Loimer et al. [18] showed that midazolam shortened the seizures to a duration which was not therapeutically desirable. Q'Reardon et al. [19] investigated benzodiazepines for postictal agitation (PIA) in a ten-patient series, and their findings revealed a resistant agitation to the intravenous administration of benzodiazepines. Despite the use of benzodiazepines for sedation, these drugs increase the seizure threshold and decrease the seizure duration and the potential efficacy of ECT [20]. In the present study, midazolam kept seizure activity lasting long enough and also suppressed post-ECT agitation efficiently, in contrast to the earlier reports [18,20]. The effects of midazolam on MAP, HR, patients' satisfaction, and recovery times were similar in group Dex and group C ($P > 0.05$).

Both dexmedetomidine and midazolam premedication significantly prevented agitation in patients who had previously shown severe post-ECT-agitation. Droperidol, propofol, promethazine, and midazolam have been studied for severe post-ECT agitation. The results suggest that these drugs can be used to prevent post-ECT agitation [12,15,19]. It is important to emphasize that even promethazine is a highly effective treatment for post-ECT agitation. However, it is a dopamine blocker, and thus can cause extrapyramidal effects and neuroleptic malignant syndrome [15].

There have been two other trials which aimed to understand the effect of dexmedetomidine in ECT. Fu and White [21] demonstrated that a single 0.5 or 1 $\mu g \cdot kg^{-1}$ dose of dexmedetomidine slightly lengthened the duration of electroencephalographic seizures. Different from Fu and White's study, we found that dexmedetomidine did not prolong the recovery time. It is possible that the higher dose of succinylcholine in the Fu and White [21] study (1.3–1.5 $mg \cdot kg^{-1}$; 0.5 $mg \cdot kg^{-1}$ in our study) may have affected the result.

Begec et al. [22] reported that acute hyperdynamic responses to ECT may be prevented by dexmedetomidine 1 $\mu g \cdot kg^{-1}$ administered over 10 min before the induction of anesthesia with propofol without altering the duration of seizure activity and recovery time. In our study, there was no need to treat hypotension with crystalloid solutions or ephedrine, and no need to treat bradycardia with atropine. It is conjectured that the reasons we found no hypotension or bradycardia may

have been the method of administration (given over a 10-min period) and the low single doses of dexmedetomidine and midazolam.

Begec et al. [22] maintained that the effect of lengthening the seizure duration was related to the age of the patients. Contrary to Begec et al. [22], despite the old age of their patient population, Fu and White [21] stated that dexmedetomidine slightly extended the duration of seizure activity during ECT. There is another explanation of the tonic-clonic motor activity being extended in dexmedetomidine-treated patients. The very low dose of titrated propofol may have caused the extended tonic-clonic motor activity in our group Dex.

In our study, the convulsive activity was determined via observation of the tonic-clonic motor activity of the patients' extremities, without the isolated cuff technique. There is a limitation of the technique that we used. McCormick and Saunders [23] reported that it must be remembered that central seizure duration monitored by electroencephalogram may outlast peripheral clonic manifestations. Therefore, it is estimated that peripheral tonic-clonic measurement may indicate a longer central seizure duration. However, the isolated cuff technique or EEG monitoring could have resulted in more reliable observation and evaluation of seizure-related motor activity or electrophysiological seizure activity.

Premedication with low-dose dexmedetomidine could be a good alternative drug to midazolam in the ECT process, with a better convulsive activity profile and lower propofol dose requirement. Dexmedetomidine and midazolam each attenuated the post-ECT agitation. Therefore, it can be concluded that a low dose of either dexmedetomidine or midazolam could be proposed for managing treatment-resistant agitation after ECT without altering the satisfaction or recovery times of the patients.

References

1. Ding Z, White PF. Anesthesia for electroconvulsive therapy. Anesth Analg. 2002;94:1351–64.
2. Hayashi Y, Maze M. Alpha 2 adrenoceptor agonists and anaesthesia. Br J Anaesth. 1993;71:108–18.
3. Rasmussen KG, Knapp RG, Biggs MM, Smith GE, Rummans TA, Petrides G, Husain MM, O'Connor MK, Fink M, Kellner CH. Data management and design issues in an unmasked randomized trial of electroconvulsive therapy for relapse prevention of severe depression: the Consortium for Research in Electroconvulsive Therapy trial. J ECT. 2007;23:244–50.
4. Swartz CM. Electroconvulsive therapy emergence agitation and succinylcholine dose. J Nerv Ment Dis. 1990;178:455–7.
5. Liston EH, Sones DE. Postictal hyperactive delirium in ECT: management with midazolam. Convuls Ther. 1990;6:19–25.
6. Auriacombe M, Reneric JP, Usandizaga D, Gomez F, Combourieu I, Tignol J. Post-ECT agitation and plasma lactate concentrations. J ECT. 2000;16:263–7.
7. Fu W, Stool LA, White PF, Husain MM. Is oral clonidine effective in modifying the acute hemodynamic response during electroconvulsive therapy? Anesth Analg. 1998;86:1127–30.
8. Simpson KH, Halsall PJ, Carr CM, Stewart KG. Propofol reduces seizure duration in patients having anaesthesia for electroconvulsive therapy. Br J Anaesth. 1988;61:343–4.
9. Wijeysundera DN, Naik JS, Beattie WS. Alpha-2 adrenergic agonists to prevent perioperative cardiovascular complications: a meta-analysis. Am J Med. 2003;114:742–52.
10. Labbate LA, Miller JP. Midazolam for treatment of agitation after ECT. Am J Psychiatry. 1995;152:472–3.
11. Devanand DP, Sackeim HA. Use of increased anesthetic dose prior to electroconvulsive therapy to prevent postictal excitement. Gen Hosp Psychiatry. 1992;14:345–9.
12. Hines AH, Labbate LA. Combination midazolam and droperidol for severe post-ECT agitation. Convuls Ther. 1997;13:113–4.
13. Grant SA, Breslin DS, MacLeod DB, Gleason D, Martin G. Dexmedetomidine infusion for sedation during fiberoptic intubation: a report of three cases. J Clin Anesth. 2004;16:124–6.
14. Fink M. Post-ECT delirium. Convuls Ther. 1993;9:326–330.
15. Vishne T, Amiaz R, Grunhaus L. Promethazine for the treatment of agitation after electroconvulsive therapy: a case series. J ECT. 2005;21:118–21.
16. Sato M, Tanaka M, Umehara S, Nishikawa T. Baroreflex control of heart rate during and after propofol infusion in humans. Br J Anaesth. 2005;94:577–81.
17. Moscrip TD, Terrace HS, Sackeim HA, Lisanby SH. Randomized controlled trial of the cognitive side-effects of magnetic seizure therapy (MST) and electroconvulsive shock (ECS). Int J Neuropsychopharmacol. 2006;9:1–11.
18. Loimer N, Hofmann P, Chaudhry HR. Midazolam shortens seizure duration following electroconvulsive therapy. J Psychiatr Res. 1992;26:97–101.
19. O'Reardon JP, Takieddine N, Datto CJ, Augoustides JG. Propofol for the management of emergence agitation after electroconvulsive therapy: review of a case series. J ECT. 2006;22:247–52.
20. Taylor S. Electroconvulsive therapy: a review of history, patient selection, technique, and medication management. South Med J. 2007;100:494–8.
21. Fu W, White PF. Dexmedetomidine failed to block the acute hyperdynamic response to electroconvulsive therapy. Anesthesiology. 1999;90:422–4.
22. Begec Z, Toprak HI, Demirbilek S, Erdil F, Onal D, Ersoy MO. Dexmedetomidine blunts acute hyperdynamic responses to electroconvulsive therapy without altering seizure duration. Acta Anaesthesiol Scand. 2008;52:302–6.
23. McCormick AS, Saunders DA. Oxygen saturation of patients recovering from electroconvulsive therapy. Anaesthesia. 1996;51:702–4.