Dexmedetomidine in premedication to attenuate the acute hyperdynamic response to ECT: a randomised, double-blind, controlled study

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Background: The choice of anaesthetic agent for electroconvulsive therapy (ECT) depends on seizure duration, haemodynamic and recovery parameters. The aim of the study was to assess the effects of dexmedetomidine premedication on haemodynamic, seizure duration, recovery characteristics and agitation following ECT.

Material and method: 60 patients aged 18–60 years scheduled for ECT were enrolled in the study. Dexmedetomidine (0.5 µg/kg) diluted to 10 ml with 0.9% saline or 10 ml 0.9% saline (control) were infused intravenously over 10 min before induction of anaesthesia with thiopentone. Motor seizure duration, heart rate, mean arterial blood pressure, time to spontaneous respiration, obeying verbal commands and post-ECT agitation score were recorded. Statistical analysis was carried out using MS Excel and Primer of Biostatistics.

Results: Post-ECT rise in mean arterial blood pressure (MAP) and heart rate (HR) in the dexmedetomidine group was significantly less ($p < 0.001$) compared with the control group at 1, 3, and 5 mins. Motor seizure duration was comparable in both groups. Mean agitation score was significantly low in the dexmedetomidine group (1.5 ± 0.50) compared with the control group (1.93 ± 0.52).

Conclusion: A dexmedetomidine dose of 0.5 µg/kg IV administered over 10 min before the induction of anaesthesia may be useful in preventing the acute hyperdynamic responses to ECT and post-ECT agitation without altering the duration of seizure activity and recovery time.

Keywords: anaesthesia, dexmedetomidine, ECT

Introduction

Electroconvulsive therapy (ECT) is very effective for many psychiatric disorders such as severe depression, schizophrenia and bipolar disorder. All ECTs are performed under general anaesthesia with neuromuscular blockade. The goals during general anaesthesia for ECT are to produce an unconscious patient with muscle paralysis and amnesia.[1] ECT is associated with hyperdynamic response due to increased concentrations of catecholamine. Increase in catecholamine leads to an acute rise in heart rate and blood pressure. This acute hyperdynamic response may lead to cardiac dysrhythmias, myocardial ischemia and infarction. To attenuate this acute hyperdynamic response, many pharmacological agents such as beta blockers, calcium channel blockers, alpha2-agonists, direct-acting vasodilators and local anaesthetics were tried.[2–5]

Dexmedetomidine is a potent as well as highly selective α2-adrenergic agonist with a sedative, sympatholytic and analgesic effect. It has been described as a safe and effective additive in many anaesthetic applications and analgesic techniques.[6]

The physiological response resulting from the stimulation of α2-adrenergic receptors varies and depends on their location in the central nervous system (CNS). Their stimulation decreases calcium entry in the nerve terminals resulting in an inhibitory effect on neurotransmitter release thus facilitating analgesia and attenuating stress response. Dexmedetomidine is used to attenuate the stress response for haemodynamic stability and to reduce the dose of anaesthetic agent.[7,8] For ECT, the optimal seizure duration remains unclear. An adequate seizure in ECT is defined as one that lasts longer than 30 sec. Too short (< 10 sec) or too long (>120 sec) may reduce clinical efficacy.[9,10] Emergence agitation (excitement, restlessness and panic) may occur in some patients after ECT.[10] Dexmedetomidine is effective in the management of emergence agitation following ECT.[5] The aim of our work is to study the efficacy of dexmedetomidine used in premedication for attenuating hyperdynamic response to ECT and along with this its effect on seizure duration, recovery characteristics and agitation following ECT.

Material and methods

After institutional ethics committee approval, 65 patients scheduled for ECT were evaluated using inclusion and exclusion criteria, and 60 patients were enrolled in this prospective randomised double blind controlled study (Figure 1). The patients were informed about the procedure and the study. Informed consent was obtained from the patients and caretakers in the prescribed form. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. Inclusion criteria were as follows: patients scheduled for ECT, physical status ASA I and II, age between 18 and 60 years, without a history of cardiovascular disease, no history of using beta-receptor blocker drugs or narcotic usage and should not be sensitive to dexmedetomidine.

The exclusion criteria included serious physical disease, baseline bradycardia (HR < 50 beats/min) such as cardiovascular disease, cerebrovascular disorder, intracranial hypertension, respiratory tract disease, previous fracture, glaucoma, arterial aneurysm, history of seizures, ASA III–V physical status, history of allergy to the study drugs and pregnancy.

Chronic antidepressant medications were continued. The patient was kept nil by mouth for at least 8 h and patients were encouraged to empty their bladder before ECT.
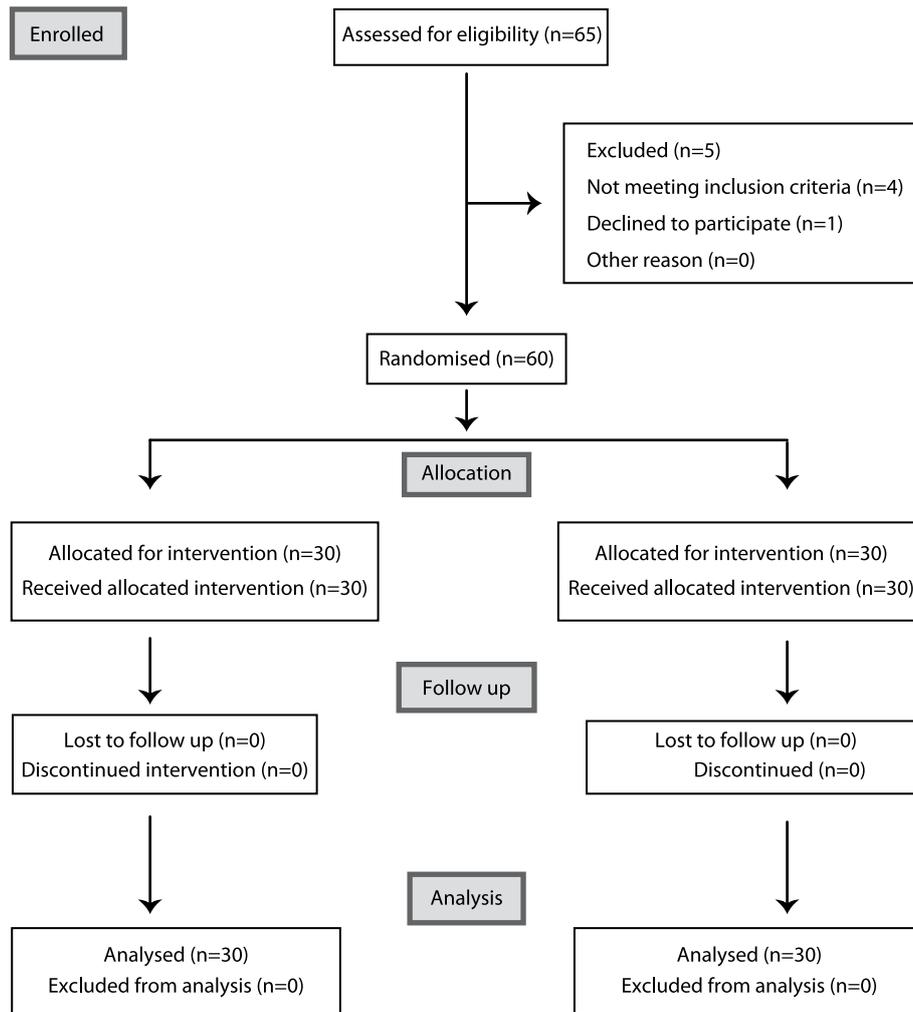
Enrolled

Assessed for eligibility (n=65)

Excluded (n=5)

Not meeting inclusion criteria (n=4)

Declined to participate (n=1)

Other reason (n=0)

Randomised (n=60)

Allocation

Allocated for intervention (n=30)
Received allocated intervention (n=30)

Allocated for intervention (n=30)
Received allocated intervention (n=30)

Follow up

Lost to follow up (n=0)
Discontinued intervention (n=0)

Lost to follow up (n=0)
Discontinued (n=0)

Analysis

Analysed (n=30)
Excluded from analysis (n=0)

Analysed (n=30)
Excluded from analysis (n=0)
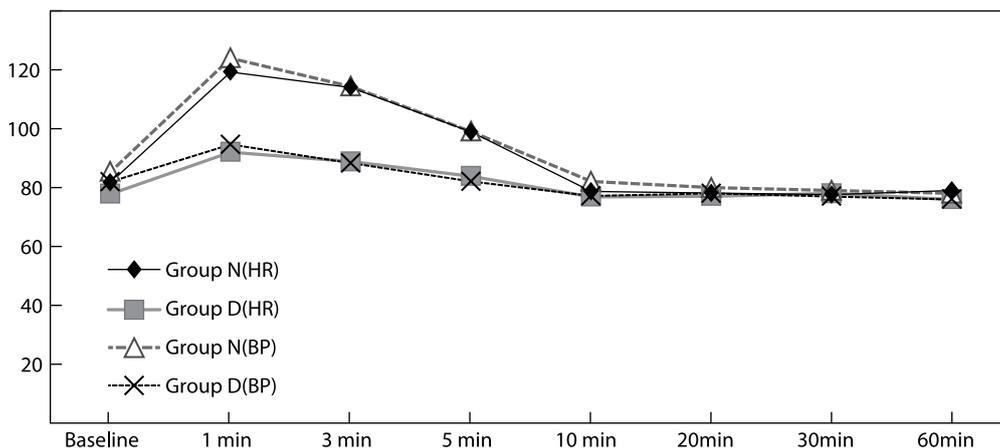
Figure 1: Consort 2010 flow diagram.

Figure 2: Post-ECT changes in heart rate and mean arterial blood pressure.

After premedication with ondansetron 4 mg and glycopyrrolate 0.2 mg intravenously, 0.5 μg/kg dexmedetomidine (diluted to 10 ml with 0.9% saline) for the dexmedetomidine group (Group D) or 10 ml 0.9% saline for the control group (Group N) was given intravenously over 10 min before induction of anaesthesia by an anaesthesiologist not involved in the recording of data. The patient was pre-oxygenated with 100% oxygen. All patients were induced with thiopentone 3 mg/kg. Induction was confirmed by loss of eyelash reflex. Succinylcholine in a dose of 0.5 mg/kg was administered after induction of anaesthesia and manual ventilation was done with a face mask using 100% oxygen at a flow rate of 8 L/min. A bite block was used to protect the patient's teeth, lips and tongue. ECT was given using a constant-current ECT device with a current of 120 mC and frequency of 70 HZ and duration 0.1 s. A stimulus was given via bifrontotemporal electrodes and ventilation was assisted with oxygen during and

after the procedure. Mean arterial blood pressure (MAP), heart rate (HR) and oxygen saturation was recorded at baseline, 1, 3, 5, 10, 20, 30 and 60 min after ECT. Peak heart rate after ECT was also noted.

The duration of the motor seizure was defined as the time from the beginning of ECT to cessation of tonic–clonic motor activity in the 'isolated' arm. The time from the end of succinylcholine administration until spontaneous breathing and obeying verbal commands was also recorded. Agitation score was evaluated after 30 min post-ECT in the post anaesthetic care unit (PACU). The agitation was evaluated using an emergence agitation score in which 1 = sleeping, 2 = awake and calm, 3 = irritable and crying, 4 = inconsolable crying, 5 = severe restlessness and disorientation.[5]

Probable side effects including nausea, vomiting, bradycardia, tachycardia, hypotension/hypertension, respiratory depression and hypoxemia were recorded after the electrical stimulus until the patient was discharged from the post-anaesthetic care unit (PACU) to the psychiatry ward. Standard monitoring was applied during recovery and the patient observed for 2 h in PACU before being moved to the ward. Respiratory depression was defined as respiratory rate less than 10 breaths/min, hypoxaemia was defined as oxygen saturation (SpO2) of 90% or less, bradycardia was defined as HR less than 50 beats/min, tachycardia as HR more than 120 beats/min, hypotension defined as MAP less than 60 mmHg, and hypertension as MAP more than 120 mmHg.

The primary outcome of the study was the efficacy of dexmedetomidine to attenuate post-ECT hyperdynamic response and a secondary outcome was studied in terms of its effect on motor seizure duration, recovery parameters and post-ECT agitation.

Sample size calculation was done by using Winpepi software in which we referred to the mean and standard deviation of a previous study by Shams and El-Masry.[5] We took a level of significance of 5% and power of study of 80%. From these calculations the exact sample size calculated was 23 for each group. Catering for willingness of the patient, inclusion–exclusion criteria and loss to follow-up, we took a sample size of 30 in each group.

Data were expressed as mean ± standard deviation. Quantitative variables are presented as mean ± SD and a t-test was used to compare significance between the two groups. Qualitative data were expressed as number (%) and analysed using a chi-square test. A p-value of < 0.05 was taken as significant. Data were analysed using Microsoft Excel® (Microsoft Corp, Redmond, WA, USA) and the software Primer of Biostatistics 6.0.

Results

Demographic variables were comparable in both the groups (Table 1).

Motor seizure duration, time to spontaneous breathing and time to respond to verbal commands were comparable in both groups while mean agitation score and peak heart rate were significantly high in Group N (Table 2).

An agitation score of 3 was observed in 3 (10%) patients in group N while none of patient in group D had an agitation score of 3. Significantly more patients in Group D had an agitation score of 1 as compared with Group N (Table 3).

No significant side effects were observed in either group (Table 4).

Table 1: Demographic data

Variable	Group N	Group D	p-value	Significance
Age (yrs)	37.47 ± 8.54	35.7 ± 7.97	0.410	Not significant
Gender (M/F)	16/14	13/17	0.440	Not significant
Body weight (kg)	61.67 ± 8.18	60.23 ± 5.57	0.430	Not significant

Table 2: Motor seizure duration and recovery characteristics

Variable	Group N	Group D	p-value	Significance
Motor seizure duration (sec)	22.9 ± 6.47	25 ± 70.205	0.205	Not significant
Time to spontaneous breathing (sec)	121.83 ± 49	125 ± 47.54	0.750	Not significant
Time to respond to verbal commands (sec)	329.67 ± 47.38	343.33 ± 33.56	0.389	Not significant
Mean agitation score	1.93 ± 0.52	1.5 ± 0.50	0.0018	Significant
Peak heart rate	124.1 ± 20.54	97.46 ± 9.5	0.000	Highly significant

Table 3: Agitation score

Agitation score	Group N (n = 30)	Group D (n = 30)	p-value
1	5 (16.7%)	15 (50%)	0.014
2	22 (73.3%)	15 (50%)	0.111
3	3 (10%)	0	0.236
4	0	0	–

Table 4: Side effects

Side effect	Group N (n = 30)	Group D (n = 30)
Nausea/vomiting	1 (3.3%)	–
Bradycardia	–	1 (3.3%)
Hypotension	–	–
Respiratory depression	–	–
Hypoxemia	–	–

Table 5: Post-ECT changes in heart rate in group N and group D

Heart rate (beats/min)	Group N	Group D	p-value
Baseline	81.73 +/– 11.8	77.86 +/– 12	0.231
1 min	119.26 +/– 14	92.03 +/– 13.5	< 0.001
3 min	114.03 +/– 12.29	88.87 +/– 12.8	< 0.001
5 min	98.9 +/– 9.65	83.86 +/– 10.58	< 0.001
10 min	78.99 +/– 10	76.86 +/– 9.3	0.396
20 min	77.12 +/– 7.81	76.21 +/– 10.1	0.912
30 min	76.56 +/– 8.17	75.57 +/– 7.91	0.635
60 min	76 +/– 7.71	75.67 +/– 8.3	0.874

Rise in heart rate and mean arterial blood pressure was significantly less in Group D as compared with Group N (Figure 2).

Table 6: Post-ECT changes in mean arterial blood pressure in Group N and Group D

MAP (mmHg)	Group N	Group D	*p*-value
Baseline	85.36 +/− 9.34	81.93 +/− 7.8	0.128
1 min	123.96 +/− 15.94	94.6 +/− 12.2	< 0.001
3 min	114.33 +/− 13.8	88.3 +/− 11.02	< 0.001
5 min	99.03 +/− 9.10	82.03 +/− 10.06	< 0.001
10 min	82.03 +/− 10.73	77.16 +/− 8.97	0.061
20 min	81.66 +/− 9.97	78.13 +/− 9.97	0.176
30 min	80.87 +/− 10.73	77.56 +/− 12.7	0.201
60 min	81.31 +/− 9.76	77.71 +/− 11.7	0.281

Post-ECT heart rate and mean arterial blood pressure were significantly higher in the control group compared with the dexmedetomidine group at 1, 3 and 5 min (Tables 5 and 6). Peak HR was lower in the dexmedetomidine group compared with the control group (*p* < 0.001 [highly significant]). Motor seizure duration in the control group (22.9 ± 6.47 seconds) was similar to that in the dexmedetomidine group (25 ± 70.205 seconds) (*p* > 0.05). Time to spontaneous breathing and obeying commands was not different between the two groups. The agitation score was significantly less in the dexmedetomidine group.

Discussion

ECT induces generalised tonic–clonic epileptic seizure. An electric current is applied transcutaneously to the brain via two electrodes positioned either bilaterally or unilaterally. A variety of adverse physiological and physical effects occur.[2] Cardiovascular and central nervous system responses are potentially most dangerous. In the central nervous system, there is an increase in intracranial pressure, cerebral blood flow, blood–brain permeability, cerebral oxygen consumption and glucose utilisation. Headache, confusion and transient memory loss were also observed after ECT. In the cardiovascular system (CVS), the initial brief parasympathetic response lasts 10–15 sec causing bradycardia, hypotension or even asystole. This initial response is followed by a sustained sympathetic response peaking at 3–5 min associated with the release of catecholamine, rise in systolic blood pressure (30–40%) and rise in heart rate (> 20%). All this predisposes to cardiac dysrhythmias, myocardial ischaemia and infarction. Even in a normal heart, ventricular dysfunction has been noted up to 6 h after ECT.[12–18] Rapid short-acting opioid analgesics and beta blockers also possess a sympatholytic effect and have recently been investigated as adjuvants during ECT[18,19] but many of them have been found to reduce seizure duration. The purpose of our study was to blunt the haemodynamic insult associated with ECT using dexmedetomidine.

Anaesthetic agents for ECT include thiopentone, propofol, ketamine, methohexitone, remifentanil, etomidate and sevoflurane.[2–5] The choice of anaesthetic agent may influence seizure quality and duration, haemodynamic and recovery parameters. For induction of anaesthesia, we used thiopentone as it has minimum effect on haemodynamic and seizure duration.[20]

Dexmedetomidine exhibits sedative and anxiolytic properties via activation of the adrenergic receptor in the locus coeruleus causing inhibition of adenylyl cyclase. This results in stimulation of parasympathetic outflow and inhibition of sympathetic outflow overall causing reduction in CVS and CNS excitation. Dexmedetomidine has been reported to be effective in ECT without serious side effects. In our study post-ECT hyperdynamic response was significantly less in the dexmedetomidine group. Heart rate and mean arterial blood pressure were significantly less at 1, 3 and 5 min in group D compared with group N. This observation was similar to the findings of Begec *et al*.[8] Begec *et al.* found that heart rate and MAP values were lower in a dexmedetomidine group at 0, 1, 3 and 10 min. Shams and El-Masry also had similar results as MAP and heart rate were on the lower side in a dexmedetomidine group as compared with a control group, in this study a combination of ketamine and propofol was used for induction.[5]

Dexmedetomidine is emerging in the literature as an agent to manage severe post-ECT agitation due to its sedative and anxiolytic properties. In our study, the agitation score was also significantly less in the dexmedetomidine group (1.5 ± 0.50 sec) compared with the control group (1.93 ± 0.52 sec). This observation was similar to those of Shams and El-Masry, Mizrak *et al.* and Cohen and Stewart.[5,7,11] Shams and El-Masry found that the number of patients with an agitation score of > 2 was significantly lower in the dexmedetomidine group (1.4%) compared with the control group (8.6%). Fiftteen (50%) patients in the dexmedetomidine group were comfortably sleeping (no hypoxaemia or respiratory depression) at the end of half an hour as compared with 5 (16.6%) patients in the control group. Three (10%) patients in the control group had an agitation score of 3 as compared with the dexmedetomidine group in which no patient had an agitation score of 3.

Motor seizure duration, time to spontaneous breathing and obeying commands were comparable between both groups. No significant side effects were observed in either group.[21] These findings were similar to those of Shams and El-Masry, Mizrak *et al.*, Begec *et al.* and Cohen and Stewart.[5,7,8,11]

Conclusion

Dexmedetomidine is effective in attenuating acute hyperdynamic response to ECT without altering seizure duration and recovery from anaesthesia, with the added benefit of decreasing post-ECT agitation.

Limitations of study

This was a controlled study and we did not compare its effect with other agents such as short-acting opioids or beta blockers used for attenuating a hyperdynamic response. EEG seizure duration was not recorded, but only that of motor seizure duration. Seizure duration can be recorded more accurately with EEG. Patient satisfaction was not recorded. The difference in requirement of thiopentone for induction in each group was not studied.

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