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Comparative Cross-Over Double Blinded Study of Two Bolus Dose of Esmolol in Preventing Hemodynamic Fluctuation during Modified ECT. (500µgm/Kg & 1000µgm/Kg)

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Abstract: ***Electro convulsive therapy (ECT) is used in the treatment of Psychiatric illness, primarily major affective disorders and certain cases of schizophrenia (1). This therapy works by electrically inducing grand mal seizures. Electroconvulsive therapy is known for its well-described, brief parasympathetic stimulation followed by adrenergic outflow during the seizure, which markedly increases heart rate (HR) (2-6) ,arterial blood pressure (6,7) , and plasma levels of catecholamine (8-10).These changes can produce cardiovascular stress. This adrenergic response can be blunted effectively by β-adrenergic blocking drugs (11, 12). Of the β-blockers studied, esmolol seems uniquely suited to blocking the effects of adrenergic outflow during ECT based on its quick onset and short duration of action (13). A number of investigators have documented esmolol's ability to blunt the increases in HR and arterial blood pressure associated with ECT, using either a single bolus or an infusion at a variety of doses (6, 11, 14-17). In studies it is found that a large premedication dose of esmolol (2.9 mg/kg) for ECT decreased the duration of seizure by 27% as measured by electroencephalogram (EEG). Whether this effect is clinically relevant is not known (5, 18), but it would be ideal to give the smallest dose of esmolol that would be clinically effective in blunting the adrenergic consequences of ECT to minimize any other potentially unwanted effects of the drug. A very low dose of esmolol 1-mg/kg bolus (6, 16), does not influence duration of seizure.***

Keywords: Electroconvulsive therapy, hemodynamic stress response, ultra short acting β-blocker esmolol, 1000µgm/kg and 500µgm/kg intra venous bolus.

TABLE I	Exclusion criteria
Pregnant women	
Less than 12 yr and more than 60yr	
AV conduction blocks greater than 1st degree.	
Systolic BP < 100 mmHg or diastolic BP < 50 mmHg	
Heart rate < 50 bpm.	
Bronchospasm or bronchial asthma.	
Drug allergy or idiosyncrasy to beta-adrenergic drugs.	
Patients on beta blockers or calcium channel blockers	

1. Methods

This study was approved by the Ethical Committee of our institution and written informed consent was obtained from each patient or legal guardian. The study patients were ASA physical status I, II, or III and selected from those receiving general anaesthesia for ECT. Exclusion criteria are listed in Table I. All patients received premedication with glycopyrrolate 0.2 mg IM 30-60 minute before ECT. The HR was monitored by ECG, BP by automated NIBP at 3 minute interval, oxygen saturation by pulse oximeter, carbon dioxide by end-tidal CO2 monitor, and seizure duration by EEG. Recording times for HR and BP did not occur during the actual seizure period. 30 patients undergoing ECT under general anesthesia in the year 2015 from January to December were randomly subjected into 3 modalities of anesthetic management. All the patients were initially pre-oxygenated with 100% oxygen and Esmolol (or placebo) was administered at time zero by hand-held 10ml bolus over 15 sec, one minute before induction of anesthesia and exactly two minutes before ECT. Anesthesia was induced with propofol 1mg/kg. Group I received Esmolol 1mg/kg IV, group II received Esmolol 0.5 mg/kg IV and group III (Control group) received normal saline (placebo). All patients received Esmolol 1000 µgm/kg, 500 µgm/kg, and placebo (normal saline) in a prospective, randomized, double-blind, within-patient, and crossover design. Thus, each patient served as his or her own control (total number of ECT were 90 setting). The anesthesiologist and the data collector were blinded of the test drug used. After the administration of the test drug in one arm, the other arm was isolated by inflating a BP cuff above the systolic BP and then the patients were given succinylcholine 0.75mg/kg and slightly hyperventilated. An oral soft bite block was placed and ECT shock current was applied after 2 minutes from the time of administration of the test drug. A Monitored Electroconvulsive Therapy Apparatus (MECTA) using bilateral stimulation was used to deliver the electrical stimulus via electrodes placed to the patient's forehead. All patients received the same electrical shock current for each ECT and received only one shock per treatment (70Hz, with 1.5 msec pulse width and 2.0 sec duration). Controlled or assisted ventilation was continued with 100 % oxygen until adequate spontaneous respiration returned. . The HR and BP were recorded pre-bolus and every 3 minute for ten minutes post-bolus, then at 12 and 15, min following bolus injection. Three to five days later the patients crossed over to the alternative treatment [crossed over to next group] and

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repeated the procedures outlined above. All statistical analyses were performed using the statistical analysis system. T test were used to determine the relation among the treatments. A $p< 0.05$ level was set for statistical significance.

2. Results

Table 1: Comparison of heart rate Esmolol 1000µgm/kg (Group I) with placebo (Group III):

Group	Pre bolus	3 min	6 min	9 min	12 min	15 min
Placebo Group III	94.64 ±14.87	102.80 ±10.30	99.76 ±18.52	97.50 ±14.86	98.02 ±12.50	97.88±12.92
Esmolol 1000µgm/kg Group I	92.80 ±12.68	86.30 ±12.38	85.66 ±15.03	88.90 ±10.05	92.52 ±13.63	94.25±12.58
p-value	0.60	<0.0001	0.002	0.0110	0.1088	0.2748

Table 2: Comparison of Systolic blood pressure Esmolol 1000µgm/kg (Group I) with placebo (Group III):

Group	Pre bolus	3 min	6 min	9 min	12 min	15 min
Placebo Group III	160±20.27	190.67±32.88	182.48±23.38	174.24±18.47	172.58±16.02	166±15.08
Esmolol 1000µgm/kg Group I	158.8±24.15	148.50±15.64	150.89±19.58	162.44±18.63	170.82±12.92	164.50±10.86
p-value	0.835	<0.0001	<0.0001	0.016	0.6413	0.66

Table 3: Comparison of Diastolic blood pressure Esmolol 1000µgm/kg (Group I) with placebo (Group III)

Group	Pre bolus	3 min	6 min	9 min	12 min	15 min
Placebo Group III	85±12.05	108±12.25	96.38±15.47	94.13±11.23	92.11±12.09	88.78±15.16
Esmolol 1000µgm/kg Group I	87.50±11.08	92±10.18	86.15±12.35	88.80±08.12	88.16±11.15	86.13±08.18
p-value	0.406	<0.0001	0.0064	0.0395	0.1935	0.4029

Table 4: Comparison of heart rate Esmolol 500µgm/kg (Group II) with placebo (Group III)

Group	Pre bolus	3 min	6 min	9 min	12 min	15 min
Placebo Group III	96.64 ±14.87	102.80 ±10.30	102.05 ±15.52	97.50 ±14.86	98.02 ±12.50	97.88 ±12.92
Esmolol 500µgm/kg Group II	98.80 ±13.68	92.25±11.32	95.02±11.50	93.76±15.91	96.06 ±09.05	99.66 ±10.50
p-value	0.560	0.0004	0.0509	0.3506	0.4894	0.5604

Table 5: Comparison of Systolic blood pressure Esmolol 500µgm/kg (Group II) with placebo (Group III):

Group	Pre bolus	3 min	6 min	9 min	12 min	15 min
Placebo Group III	160.88±16.27	190.67±32.88	184.48 ±21.38	174.24±18.47	172.58±16.02	166±15.08
Esmolol 500µgm/kg Group II	154.96±12.50	162.56±22.48	174.12±15.05	170.96±15.12	168.02±11.55	162.86±18.02
p-value	0.1195	0.0003	0.0341	0.4547	0.2111	0.467

Table 6: Comparison of Diastolic blood pressure Esmolol 500µgm/kg (Group II) with placebo (Group III):

Group	Pre bolus	3 min	6 min	9 min	12 min	15 min
Placebo Group III	88.32±10.05	108±12.25	102±10.47	94.13 ±11.23	92.11 ±12.09	90±12.16
Esmolol 500µgm/kg Group II	82.93±18.25	102.52 ±15.12	98.82±08.52	96 ±08.00	96.24 ±10.22	92.21 ±06.58
p-value	0.1618	0.1284	0.2021	0.4606	0. 1584	0.3849

3. Discussion

Electroconvulsive therapy (ECT) is an important modality in the treatment of depression, especially in severe cases resistant to pharmacologic therapy. It has been used for almost half a century. During this time there have been significant improvements in ECT application methods and also in patient management including anesthetic technique. Central Nervous system seizure activity rather than electrical stimulus is responsible for the beneficial effect of ECT but the exact mechanism of the therapeutic effects is not yet understood.15,17,19,20. ECT is often associated with significant hypertension, tachycardia, and an increase in cardiac output. A hyper-dynamic cardiovascular response occurs as a result of central activation of the autonomic nervous system. A brief parasympathetic discharge occurs immediately (during the first 10 to 15 seconds after the application of electrical current, during the tonic phase of the seizure) with a sympathetic discharge following within seconds. Within 10 to 12 seconds of the sympathetic surge, caused by epinephrine and norepinephrine release, sinus tachycardia and arterial hypertension may develop. Plasma epinephrine increases to 15 times normal levels, and plasma

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norepinephrine peaks can become 3 times higher than under normal resting conditions, with peak levels occurring within 60 seconds of electrical stimulation21.22.23. Studies have shown that the concentration of epinephrine decrease towards normal values 10 minutes after ECT, and norepinephrine levels remain increased for twice as long. These hemodynamic changes produce an abrupt increase in myocardial oxygen consumption21,22.23. Therefore it may be beneficial to administer a short acting beta-blocker to blunt the catecholamine stress response. A cardiovascular mortality rate of 0.03% has been reported with ECT5. In patients with preexisting cardiovascular disease, the acute hemodynamic response to ECT may increase the risks of myocardial ischemia and infarction and even cardiac rupture. Although rare, cardiovascular complications are the main cause of death during ECT with a mortality rate of 0.03% of patients treated, and 0.0045% of individual ECT treatments 15,24,5. This is higher than the often quoted overall anesthetic mortality of 1:10,000 25. Similar to techniques used for tracheal intubation, many pharmacologic methods have been used in an attempt to blunt the hemodynamic effects of ECT. These include many antihypertensive drugs given by various routes (including trimethaphan, nitroprusside, nitroglycerin, propranolol, alprenolol, esmolol, labetalol, clonidine, dexmedetomidine, urapidil, and nicardipine) However, the ideal pretreatment regimen to attenuate the acute hemodynamic response after ECT has not been identified. The ideal agent for attenuating the hyper-dynamic response of ECT would be convenient, easily available, easy to prepare and administer, rapid acting, brief, non-toxic, and have minimal or no side effects15,17, 26-31. Esmolol hydrochloride is an ultra-short acting, beta-one selective adrenergic receptor blocker with a distribution half-life of two minutes and an elimination half-life of nine minutes. Esmolol appears quite suitable for use during a short-lived stress such as tracheal intubation or ECT. Administration of esmolol by bolus and infusion has been found to be effective in blunting the hemodynamic effects of laryngoscopy and intubation as well as intraoperative and postoperative stresses. These pharmacokinetics of this drug make it suitable for use during induction to blunt the stress response to ECT which can occur up to 10-15 minutes after the application of the stimulus, as it may take 10-20 minutes for the level of epinephrine and norepinephrine to come down to its normal level after ECT 21-23. We have studied the hemodynamic response to Esmolol 1000µgm/kg and 500µgm/kg after ECT for a period of fifteen minutes as this was the average period of hemodynamic changes after ECT. We have found that 1mg/kg of Esmolol was effective in blunting the rise in mean HR, systolic BP up to 9 minutes and also reduction of mean diastolic BP up to 9 minutes. Kovac et al have found that 100 and 200 mg bolus doses of Esmolol significantly blunted the maximum increase in heart rate and mean arterial pressure following ECT in comparison to placebo. They also noted that there was a significant difference in HR between the 100 mg esmolol dose and placebo for up to four minutes post-ECT and up to 18 minutes post-ECT for the 200 mg dose. This coincides with our finding that a dose like 1mg/kg of esmolol is effective in blunting the rise in HR and BP after ECT for first 9 minutes. A lower dose of 500µgm/kg significantly reduces the post ECT raise of heart rate and systolic blood pressure up to 6 minute. This dose could not produce any significant effect on mean diastolic blood pressure. A higher dose like 200 mg bolus may be effective in blunting the response for longer period but as Kovac et al have found that 200mg dose also caused a slightly shorter duration of seizure, a lower dose was considered to be better for ECT. So we conclude that a dose of 1mg/kg of esmolol is effective in attenuating the hemodynamic response to ECT for the first 9 minutes; much lower dose of 500µgm/kg is effective in attenuating hemodynamic response up to 6 minutes, but it has no effect on diastolic blood pressure. We did not evaluate the effect on seizure duration. Further studies are needed to evaluate the efficacy and safety of the therapy.

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