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Original Article

Comparative study of esmolol and labetalol to attenuate haemodynamic responses after electroconvulsive therapy

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Abstract

Objective: The study was designed to evaluate the hemodynamic effects of Esmolol and labetalol in patients undergoing electroconvulsive therapy.

Materials and Methods: Ninety patients undergoing electroconvulsive therapy treatment were studied according to randomized, double blind placebo controlled protocol. Ninety patients were divided into three groups with thirty patients in each group. Patients received either Esmolol (1mg/kg), Labetalol (0.25mg/kg) or Normal Saline (placebo) intravenously just after induction with propofol. The baseline heart rate and blood pressure were recorded. Hemodynamic parameters before and after drug therapy and after the ECT current application, were recorded at different time intervals.

Results: It was found that Esmolol significantly attenuated the degree of tachycardia and hypertension after ECT in comparison with placebo in the first three minutes ($p<0.05$), whereas the rise in HR and blood pressure was significantly blunted in the labetalol group in comparison to placebo, from three minutes onward till ten minutes. ($p<o.o5$).

Conclusion: It was concluded that Esmolol is effective in blunting the hemodynamic response after ECT stimulus in the first three minutes after application of the electrical current, whereas Labetalol is effective after five minutes onwards till ten minutes.

Key words: Electroconvulsive therapy, hemodynamic stress response, hypertension, tachycardia, sympathetic nervous system, beta adrenergic antagonists, esmolol, labetalol.

Electroconvulsive therapy (ECT) is a useful modality in the treatment of major depressive disorders. It can also be used for the management of recurrent depressive states, acute and chronic schizophrenia, acute manic states, and in certain psychosomatic disorders[1,3,4]. Historically ECT was performed without anaesthesia, but nowadays it is performed under general anaesthesia with muscle relaxation to avoid the risks of long bone and vertebral fractures from violent muscle contractions. The aim of the anaesthesiologist is to provide safe and effective anaesthesia without interfering with the beneficial effects of ECT[1].

ECT may produce intense stimulation of the central nervous system resulting in hypertension and tachycardia. The hemodynamic effects of ECT could place the patient with coronary or cerebrovascular disease at risk of myocardial ischemia/infarction or stroke[3-5]. Many pharmacologic agents have been used by various routes in an attempt to blunt the hemodynamic effects of ECT. Esmolol is a ultra-short acting beta1- selective adrenergic agent and Labetalol is an adrenergic receptor blocking agent with mild alpha1- and predominant beta –adrenergic receptor blocking action. Both these drugs have been safely used in anaesthetic practice to blunt the stress response to laryngoscopy and intubation[3]. There are also studies evaluating the effectiveness of these drugs in blunting the stress response to ECT. This study was designed to compare Esmolol and labetalol in attenuating the hemodynamic response to ECT during the first ten minutes after the application of the electrical current.

Materials and methods:

This study was conducted in the department of Anaesthesiology and IC, Kathmandu Medical College Teaching Hospital, Kathmandu.

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The study patients were ASA physical status I and II and selected from those receiving general anaesthesia for ECT. Patients with AV conduction block greater than 1st degree, heart rate less than 50bpm, systolic bp<90 mmHg, history of bronchospasm or bronchial asthma, and patients with history of drug allergy or idiosyncrasy to beta-adrenergic drugs were excluded from the study.

90 patients undergoing ECT under general anaesthesia were randomly divided into 3 groups of 30 patients each. All the patients were initially preoxygenated with 100% oxygen and then induced with propofol 1-2mg/kg immediately after the induction, the test drugs were given as a bolus. Group I received Esmolol 1mg/kg iv, group II received Labetolol 0.25 mg/kg iv and group III(Control group) received normal saline (placebo). 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 1mg/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. All patients received the same electrical shock current for each ECT and received only one shock per treatment.

A Monitored Electroconvulsive Therapy Apparatus (MECTA) using bilateral stimulation was used to deliver the electrical stimulus via electrodes placed to the patient's forehead. The effectiveness of ECT current was verified by appearance of tonic-clonic seizures in the isolated arm. Controlled or assisted ventilation was continued with 100 % oxygen until adequate spontaneous respiration returned.

HR and BP were recorded before the administration of the test drug (baseline) and 1minute after the administration. HR and BP was then recorded at 1 minute, 3 minutes, 5 minutes , and 10 minutes after the ECT shock. 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.

Results

Comparison of Esmolol with placebo

Mean heart rate, systolic BP and diastolic BP at induction with propofol in both the placebo and esmolol group was similar. The difference was statistically insignificant (p=0.29, 0.15 & 0.06 respectively). However the mean heart rate in the Placebo group, 1 minute after ECT was 93.76 ± 15.91 whereas it was only 85.73± 15.92 in the Esmolol group, the difference was statistically significant ($p<0.05$). The difference in mean heart rate in two group was also statistically significant in the three minutes after ECT (p=0.01), but the difference in mean heart rate in the two groups at 5 and 10minute after ECT were not statistically significant(p=0.15 and p=0.19 respectively). This shows that Esmolol was effective in blunting the rise in HR in the immediate period (1 minute and 3 minute) after ECT but not effective in the later period (5-10minutes later).

Similarly there was a significant difference in the mean systolic BP after 1min and 3mins of ECT application among the two groups, the mean systolic BP being lower in the Esmolol group. But there was no clinically significant difference in the mean systolic BP among the two groups at 5minutes and 10 minutes after ECT, which shows that Esmolol was effective in blunting the rise in BP after ECT in the first 3 minutes but not in the later period.

The difference in the mean diastolic blood pressure in the Esmolol group and the Placebo group in the early period after ECT (1minute, 3minute and 5 minutes after ECT) were found to be statistically significant ($p<0.05$), but not statistically significant at 10 minutes post ECT period (p value 0.28) indicating that Esmolol in comparison to placebo, prevented the rise in diastolic BP in the early period after ECT but not in the later period .

Comparison of Labetalol with placebo:

Mean HR, Systolic BP, &diastolic BP was similar during induction in both the labetalol and placebo group (the difference was not statistically significant). The mean heart rate 1 minute and 3 minutes after ECT in the two groups also was not much different (difference was statistically insignificant, $p>0.05$); but the mean heart rate in two groups after 5 minute and 10 minute post -ECT were found to be significant statistically, the HR being much higher in the placebo group, indicating that the rise in HR was blunted by labetalol at 5-10 minutes after ECT, but not in the immediate period (1-3 minutes).

Mean systolic blood pressure 1 minute after ECT in the two group was similar (the difference was statistically insignificant) but there was a statistically significant difference in the mean systolic BP in the first 3, 5, and 10 minutes after the ECT among the two groups ($p<0.05$), indicating that labetalol was not able to blunt the rise in mean arterial pressure in the early post-ECT period but was able to blunt the rise in the later period till 10 minutes after ECT.

Similarly the mean diastolic pressure in both the groups were also similar in the two groups at 1 min after ECT but there was a statistically significant difference in the mean diastolic pressure among the two groups at 3, 5, & 10 minutes from ECT, the mean diastolic BP values being higher in the placebo group, which suggests that labetalol may be effective in blunting the rise in diastolic BP after 3 minutes till 10 minutes post- ECT but not immediately post ECT (1 minute).

Table 1: heart rate at different time interval placebo vs. esmolol

Group	induction	1min drug	1minECT	3minECT	5minECT	10minECT
Placebo	83.06 ±14.87	86.30± 14.75	93.76± 15.91	99.66± 19.03	85.93± 21.66	88.83± 15.93
Esmolol	86.86 ±12.68	79.30± 12.52	85.73 ±15.92	87.93± 18.52	79.70 ±10.05	83.70± 13.89
p-value	0.29	0.05	0.05	0.01	0.15	0.19

Table 2: Systolic blood pressure at different time interval placebo vs. esmolol

Group	induction	1min drug	1min ECT	3min ECT	5min ECT	10min ECT
Placebo	124 ±21.27	98.66± 25.15	129.33± 20.66	92.66± 14.84	123.33± 23.53	122 ±23.69
Esmolol	110.66 ±19.81	93.33 ±17.48	106.00 ±27.61	106.00 ±19.58	117.33 ±23.62	113.00 ±24.23
p-value	0.15	0.34	0.00	0.04	0.32	0.15

Table 3: Diastolic blood pressure at different time interval placebo vs. esmolol

Group	induction	1min drug	1min ECT	3min ECT	5min ECT	10min ECT
Placebo	64.00 ±13.02	67.66± 15.46	88.33± 13.41	84.66± 13.32	81.00± 15.16	81.33 ±10.74
Esmolol	71.33 ±16.13	60.66 ±10.80	72.66 ±13.47	76.66 ±13.47	73.00 ±12.35	77.66± 15.24
p-value	0.05	0.04	0.00	0.02	0.02	0.28

Table 4: heart rate at different time intervals placebo vs. labetalol

Group	induction	1min drug	1min ECT	3min ECT	5min ECT	10min ECT
Placebo	83.06± 14.87	86.30± 14.75	85.93± 21.66	88.83± 15.98	93.76 ±15.91	99.66± 19.03
Labetalol	86.86 ±12.68	79.30 ±12.52	79.70 ±10.05	81.80± 15.20	85.10 ±13.09	85.73 ±11.81
p-value	0.29	0.05	0.15	0.19	0.05	0.01

Table 5: systolic blood pressure placebo vs. labetalol

Group	induction	1min drug	1min ECT	3min ECT	5min ECT	10min ECT
Placebo	122.00± 23.69	98.66± 25.15	123.33 ±23.53	124.00 ±21.27	129.33 ±20.66	92.66± 14.84
Labetalol	113.00 ±17.20	93.33 ±17.48	119.00 ±20.90	110.66 ±19.81	106.00 ±27.61	106.00 ±19.58
p-value	0.15	0.34	0.32	0.01	0.00	0.04

Table 6: diastolic blood pressure placebo vs. labetalol

Group	induction	1min drug	1min ECT	3min ECT	5min ECT	10min ECT
Placebo	64.00± 13.02	67.66± 15.46	81.33± 10.74	84.66± 13.32	88.33± 13.41	81.00 ±15.16
Labetalol	71.33 ±11.00	60.66± 10.80	77.66± 15.24	76.66± 13.47	72.66± 17.60	73.00± 12.35
p-value	0.05	0.04	0.28	0.02	0.00	0.02

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 a half century. During this time there have been significant improvements in ECT application methods and also in patient management including anaesthetic 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[1-4].

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 norepinephrine peaks can become 3 times higher than under normal resting conditions, with peak levels occurring within 60 seconds of electrical stimulation[7,11,13].

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 consumption[7,11,13]. Therefore it may be beneficial to administer a short acting beta-blocker or a mixed alpha-beta-blocker to blunt the catecholamine stress response.

A cardiovascular mortality rate of 0.03% has been reported with ECT[14]. 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[3,12,14]. This is higher than the often quoted overall anaesthetic mortality of 1:10,000[15].

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 effects[3-6, 8-11].

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. Labetolol is an adrenergic receptor blocking agent with mild alpha1- and predominant beta-adrenergic receptor blocking actions (alpha:beta blockade ratio of 1:7 for iv and 1:3 for PO administration). Onset of action of iv labetalol is 2-5 minutes with peak effect at 5-15 minutes[16]. These pharmacokinetics of these drugs 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[7,11,13].

We have studied the hemodynamic response to Esmolol and Labetolol after ECT for a period of ten 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 and systolic BP up to 3 minutes and the mean diastolic BP up to 5mins. 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 lower dose like 1mg/kg of esmolol is effective in blunting the rise in HR and BP after ECT for first 3-5 minutes. 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.

Our study found that 0.25mg/kg Labetolol is not effective in blunting the rise in mean HR, mean systolic and mean diastolic pressure in the first 3 minutes but effective after 3-5 minutes after ECT and up to 10 minutes, which coincides with the onset time and the peak onset time of the drug.

So we conclude that a dose of 1mg/kg of esmolol is effective in attenuating the hemodynamic response to ECT in the first 3 minutes whereas labetalol is effective in attenuating the response in the period from 3-10 minutes. A combination of Esmolol and labetalol given 2-3 minutes prior to ECT stimulation or a esmolol infusion may produce better HR and BP control for a longer time than the individual drugs given alone as a bolus. Further studies are needed to evaluate the efficacy and safety of the combination therapy.

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