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Comparison of two different doses of injection esmolol on haemodynamic response and seizure duration during electroconvulsive therapy

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Abstract

Introduction-This study was aimed to compare the effects of two different doses of injection esmolol on haemodynamic response during ECT. Also the effects of esmolol pre-treatment on seizure duration, duration of anaesthesia and duration of recovery from anaesthesia and adverse effects if any were observed.

Methods -Total 40 patients of ASA I or II posted for ECT were each studied thrice during three consecutive ECT treatments. Hence total of 120 ECT exposures studied. Three groups were formed

Group P received placebo; Group E1 and E2 received intravenous esmolol 12.5mg and 25 mg bolus before ECT. Heart rate (HR), systolic and diastolic blood pressure (SBP/DBP) was recorded pre-bolus and every minute for 5 min and then 10, 15, 20, 25 & 40 minutes post-bolus. Duration of seizure, duration of anaesthesia, recovery and incidence of side effects were noted.

Results- HR, SBP and DBP increased significantly in placebo group; at 5 minutes post ECT, HR in P, E1 and E2 group was (mean 145.20 ± 18.67,128.98 ± 17.72, 121.75 ± 18.38); SBP was (mean 168.85 ± 10.29, 152.88 ± 14.16, 143.90 ± 12.91) and DBP was (mean 114.45 ± 6.52, 103.35 ± 8.45, 93.05 ± 9.34) Superior hemodynamic stability was found in E2. Duration of seizure (P=0.952), duration of anaesthesia (P=0.437) and recovery (P= 0.792) had no effect of esmolol pre-treatment. No side effects were found in any of the study groups.

Conclusion- Esmolol 25mg pre-treatment has stable haemodynamic results and no effect on seizure duration thus therapeutic outcome of ECT is not affected.

Keywords: Esmolol, ECT, Hemodynamic response of two different doses, Seizure duration.

1. Introduction

Electroconvulsive therapy (ECT) is an accepted treatment modality in psychiatry. The response to electrical stimulus has significant therapeutic benefits as well as profound systemic adverse effects. The parasympathetic sequence followed by sympathetic outflow produces noradrenaline and adrenaline to increase by 3-5 folds over pre-ECT levels. [1, 2]

The resultant transient but marked increase in heart rate and blood pressure has been proved risky to patients with coronary artery and cerebrovascular diseases. This study compares the effects of two doses of esmolol hydrochloride on hemodynamic response and seizure duration during ECT.

2. Material and Methods

A prospective non-randomized clinical study with cross over design was conducted on ECT patients. Every patient was subjected to anaesthesia thrice a week using intravenous pretreatment with placebo, esmolol 12.5mg and 25mg respectively. Forty patients were studied during total 120 anaesthesia exposures. The study was conducted in a tertiary care level institute and approval of Institutional Review Board/Ethics Committee was obtained. ASA grade 1 & 2 adult patients between 20 to 60yrs, of either sex, posted for prescribed ECT treatment were studied after written informed consent obtained in their own language from their relatives.

Patients were evaluated in psychiatric ward and those with hypertension, diabetes, asthma, convulsions, allergy, jaundice or previous ECT were excluded. All pre-procedure preparation was checked and resuscitation equipment was kept ready. After confirming NBM status, consent and omitting antipsychotic drug dose prior to ECT, all patients received glycopyrrolate 0.2mg intra muscular and ondansetron 4mg intravenous 30min prior to treatment. IV line was secured and baseline blood pressure (systolic and diastolic SBP and DBP), heart rate (HR), electrocardiogram (ECG) and oxygen saturation (SpO2) were recorded and monitored prior to induction and throughout the procedure. Each patient was studied during his/her thrice a week ECT regimen after pre-medication with placebo, intravenous esmolol 12.5mg & 25mg at three respective ECT episodes.

Study drug was preloaded in a 10ml syringe. The person who was giving the study drug was not participating in the study. The person noting observations was not aware of the nature of study pre-treatment. Either placebo or esmolol 12.5mg or 25mg was given over 15 sec exactly 1 min prior to induction & 2 min prior to ECT.

Anaesthasia was induced with thiopentone (2 to 2.5mg/kg) & suxamethonium 0.5mg/kg; patients were ventilated with 100% oxygen with facemask using Magill's circuit (Mapleson A) till fasciculation subsided and muscle relaxation was achieved. A mouth gag was inserted inside the oral cavity separating tongue, teeth and buccal mucosa, to prevent any damage to the soft tissue of the oral cavity, tongue and fracture of teeth.

The electroconvulsive therapy was applied to the head through two electrodes kept on both temporo-frontal regions (bi-temporal ECT) after applying ECT gel on to the electrodes.

A brief-pulse, square-wave, constant-current ECT was applied using BPE-891 machine. (Pulse of 60 Hz with 0.8msec duration with total stimulus time of 1 sec) HR and BP were recorded pre-bolus and then every minute for 5 min and then 10, 15, 20, 25 & 40 minutes post-bolus.

Every patient was crossed over with the next dose of study drug and repeat procedure outlined as above was carried out on second and fourth day. The settings and position of the electrodes were kept constant by the psychiatrist. Each patient's ECT induced seizure threshold was determined in first two ECT sessions. These two sessions were not included in study.

HR, SBP and DBP were recorded pre procedure during pre-anaesthesia checkup, before giving study drug and ECT and every minute for 5 min then 10 min, 15 min, 20 min, 25 min and 40 min after giving study drug and ECT. Duration of seizure was recorded from the start of motor seizure to the end of the clonic contraction using a hand held stopwatch. Side effects like nausea and vomiting and specific side effects like hypotension and bradycardia were recorded till recovery. Total duration of anaesthesia was recorded from loss of eyelash reflex to return of spontaneous respiration.

Statistical Analysis: The data was managed in Microsoft excel spreadsheet. The data were expressed as mean ± SD; qualitative data variables were expressed by using frequency and percentage (%). Quantitative data variables

(like HR, SBP and DBP) were expressed by using mean and SD using ANOVA test. Chi square test / Fischer's exact test was used to find the association between occurrence of side effects within treatment groups. A p value <0.05 was considered statistically significant. All graphs were drawn and all statistical analysis was done using Statistical Package for Social Sciences (SPSS) software version 20:0

3. Observations and results

In total 40 patients were enrolled in our study. Twenty (50%) patients were of schizophrenia and 10 (25%) were of severe depressive disorder and others were bipolar affective disorder (15%) and obsessive-compulsive disorder (10%). Each patient was studied for three times during consecutive ECT treatments. Hence total 120 ECT treatments were studied. In our study, 47.50% were female patients and 52.50% were male patients. Twenty (50%) participants were of age 21 to 30 years, 8 (20%) patients were below 20 years, 7 (17.5%) between 31 to 40 and 5 (12.5%) were above 40 years. **(Table-1)**

Table-1: Demography- Age and Sex wise distribution of patients in study groups-

Psychiatric disorder	Number of patients	Percentage (%)
Schizophrenia	20	50.00
Severe Depressive Episode	10	25.00
Bipolar Affective Disorder	6	15.00
Obsessive Compulsive Disorder	4	10.00
Age in years	Number of patients	Percentage (%)
<20	8	20.00
21-30	20	50.00
31-40	7	17.50
>40	5	12.50
Total	40	100.00
Gender	Number of patients	Percentage (%)
Male	19	47.50
Female	21	52.50
Total	40	100.00

Significant difference was noted between mean heart rate in group P, group E1 and group E2 after application of ECT up to 40 minutes duration ($p < 0.05$). According to table-2 there was maximum increase in HR at 3, 4 and 5 minutes. Esmolol 25mg was more useful in reducing HR at 3, 4 and 5 minutes than esmolol 12.5mg. At 40 minutes in group P, HR did not return to pre-bolus values. With esmolol 25mg at 40 minutes HR returned to pre-bolus values (P value 0.018) **(Table-2)**

Table-2 - Comparison of heart rate in Group P, E1 and E2

HR at	Group P (n=40)		Group E1 (n=40)		Group E2 (n=40)		p-value
	Mean	SD	Mean	SD	Mean	SD	
Pre-operative	70.85	12.28	70.75	11.83	71.55	11.41	0.947
Pre bolus	73.83	12.69	73.28	12.06	74.23	11.87	0.941
1 min	101.73	14.55	95.70	12.27	90.98	11.18	0.001*
2 min	115.85	11.05	107.20	10.00	100.88	9.67	< 0.001*
3 min	128.50	9.50	117.53	10.54	112.25	11.47	< 0.001*

4 min	138.93	13.79	124.88	14.33	117.05	13.54	< 0.001*
5 min	145.20	18.67	128.98	17.72	121.75	18.38	< 0.001*
10 min	133.48	17.34	119.90	17.17	111.23	17.36	< 0.001*
15 min	118.78	12.83	108.58	14.28	100.50	13.42	< 0.001*
20 min	103.60	12.32	95.25	12.48	89.45	12.65	< 0.001*
25 min	91.40	11.04	85.58	11.32	80.15	9.39	< 0.001*
40 min	80.23	9.39	77.08	9.37	74.40	8.34	0.018*

***Significant**

ANOVA test is applied; p-value < 0.05 is significant

Systolic blood pressure in group P, group E1 and group E2 showed significant difference ($p < 0.05$). According to table-3 there was maximum increase in SBP at 3, 4 and 5 minutes. Esmolol 25mg was more useful in reducing SBP at 3, 4 and 5 minutes than esmolol 12.5mg. At 40 minutes without esmolol SBP did not return to pre-bolus values. With esmolol 25mg at 40 minutes SBP returned to pre-bolus values (P value 0.001). **(Table-3)**

Table-3 - Comparison of Systolic Blood Pressure in Group P, E1 and E2

SBP at	Group P (n=40)		Group E1 (n=40)		Group E2 (n=40)		p-value
	Mean	SD	Mean	SD	Mean	SD	
Pre-operative	110.33	8.12	110.65	7.01	110.70	7.68	0.972
Pre bolus	112.75	7.80	112.08	6.10	112.35	6.70	0.908
1 min	138.70	13.85	132.05	10.26	125.15	7.71	< 0.001*
2 min	148.55	12.03	139.25	7.51	133.40	7.64	< 0.001*
3 min	160.85	11.13	146.00	8.26	138.55	7.37	< 0.001*
4 min	163.90	25.80	152.50	9.15	142.45	10.38	< 0.001*
5 min	168.85	10.29	152.88	14.16	143.90	12.91	< 0.001*
10 min	154.45	13.62	144.70	12.90	134.75	13.74	< 0.001*
15 min	143.70	9.05	133.95	8.21	127.00	10.47	< 0.001*
20 min	133.35	8.57	126.45	9.00	120.75	9.12	< 0.001*
25 min	127.40	6.44	119.60	7.72	115.25	8.81	< 0.001*
40 min	118.70	7.81	115.45	7.56	111.85	8.51	0.001*

***Significant (ANOVA test used)**

ANOVA test is applied; p-value < 0.05 is significant

As p < 0.05, there was significant difference between diastolic blood pressure in group P, group E1 and group E2 after application of ECT. According to **table-4** there was maximum increase in DBP at 3, 4 and 5 minutes. Esmolol 25mg was more useful in reducing DBP at 3, 4 and 5 minutes than esmolol 12.5mg. At 40 minutes without esmolol DBP did not return to pre-bolus values. With esmolol 25mg at 40 minutes, DBP returned to pre-bolus values (P value 0.001).

Table-4 - Comparison of Diastolic Blood Pressure in Group P, E1 and E2

DBP at	Group P (n=40)		Group E1(n=40)		Group E2 (n=40)		p-value
	Mean	SD	Mean	SD	Mean	SD	
Pre-operative	71.28	6.23	71.45	5.53	72.25	6.89	0.758
Pre bolus	72.50	8.01	71.80	5.97	73.50	6.85	0.552
1 min	92.90	11.89	86.25	9.80	85.85	7.81	0.003 *
2 min	97.90	11.16	92.05	7.27	89.05	6.88	< 0.001 *
3 min	104.20	9.18	95.30	7.90	89.85	5.74	< 0.001 *
4 min	109.75	6.81	99.65	6.59	92.70	7.42	< 0.001 *
5 min	114.45	6.52	103.35	8.45	93.05	9.34	< 0.001 *
10 min	103.50	7.76	95.50	7.09	88.10	8.59	< 0.001 *
15 min	96.80	7.55	91.20	7.20	85.00	8.56	< 0.001 *
20 min	91.00	7.66	84.45	9.05	80.00	8.09	< 0.001 *
25 min	84.80	6.43	79.50	6.46	74.65	7.32	< 0.001 *
40 min	77.40	5.51	75.65	9.39	71.40	5.87	0.001 *

***Significant (ANOVA test used)**

ANOVA test is applied; p-value < 0.05 is significant

Table-5 shows comparison of mean seizure duration, mean duration of anaesthesia and mean time of recovery in three groups. ANOVA test was applied and p value obtained was 0.952, 0.437 and 0.792 respectively. Thus there was no significant difference of seizure duration, anaesthesia duration and recovery between groups P, E1 and E2. (p< 0.05 is significant)

Table-5 - Comparison of Seizure Duration, Total duration of Anaesthesia and Time of recovery and side effects from anaesthesia in Group P, E1 and E2

Group	Number of Patients	Seizure Duration (sec)		p-value
		Mean	SD	0.952
Group P	40	42.65	12.77	
Group E1	40	41.78	12.72	
Group E2	40	42.05	12.70	
ANOVA test applied; p value > 0.05 is insignificant.				

As p value is 0.925 there is no significant difference of seizure duration between groups P, E1 and E2.

Group	Number of patients	Duration of Anaesthesia (min)		p-value
		Mean	SD	0.437
Group P	40	10.13	1.59	
Group E1	40	9.78	1.39	
Group E2	40	9.75	1.37	

ANOVA test applied; p value > 0.05 is insignificant. As p value is 0.437 there is no significant difference in duration of anaesthesia between groups P, E1 and E2.

Group	Number of Patients	Time of Recovery (min)		p-value
		Mean	SD	0.792
Group P	40	14.18	1.38	
Group E1	40	14.33	1.40	
Group E2	40	14.13	1.30	

ANOVA test applied; p value > 0.05 is insignificant. As p value is 0.792 there is no significant difference in time of recovery from anaesthesia between groups P, E1 and E2.

Group	Number of patients	Side effects- nausea and vomiting		p-value
Group P	40	Nausea in 1	Vomiting in 1	0.999
Group E1	40	Nausea in 1	Vomiting in 1	
Group E2	40	None	None	

p-value > 0.05 (Not significant)

Fischers's exact test applied, p value > 0.05 is insignificant. As p value is 0.999 there is no significant difference in side effects between groups P, E1 and E2.

Comparison of side effects in Group P, E1 and E2 was done; p-value > 0.05 (Not significant) after applying Fischer's exact test indicates (p value is 0.999) there is no significant difference in side effects between the groups. Also specific side effects like bradycardia and hypotension were not seen in any of the three groups.

4. Discussion

ECT is an important treatment option for psychiatric patients. Esmolol, an ultra-short acting beta-1 selective agent is known to attenuate the haemodynamic response to ECT. [3, 4]

We evaluated total 40 patients; most patients were of schizophrenia (50.0%) and severe depressive disorder (25.0%) and others were bipolar affective disorder and obsessive-compulsive disorder. (Table-1)

ECT involves induction of generalized epileptic seizures for therapeutic purpose, using brief-pulse stimulation technique under anaesthesia and muscle paralysis. ECT can be the first choice of treatment in depressive stupor and inanition, as in melancholic, catatonic, or psychotic depression. Various other indications for ECT include depression, schizophrenia, mania, and schizoaffective psychosis after failure of medication treatment. [5]

In our study, 50% participants were between 21 to 30 years whereas 20% were below 20 years in contrast to the reports of Howie et al; [6] they reported mean age of 44±18 years as age may vary primarily upon the indication for ECT. Proportion of males and females was nearly similar in our study (47.5% and 52.5% respectively). Distribution of gender may also vary depending on specific indications

of ECT. In a study from Parikh et al [5] involving 30 patients of depression (43%), psychosis (43%), and bipolar disorder (14%), 13 (43.3%) were males and 17 (56.7%) were females, which is similar to our study results. (Table-1)

Heart rate at baseline and pre-bolus phase did not differ in three groups (p=0.947). Post-ECT, it increased significantly in patients who were not treated with esmolol than those who received esmolol. Though the heart rate gradually increased over next 10 minutes in all three groups, it was significantly lower in patients who received esmolol; treatment with 25 mg dose was associated with lower HR than 12.5 mg. (Table-2)

A study from Kovac et al evaluated effect of esmolol bolus (80 mg) and infusion (24 mg/min) on HR and BP reported that increase in HR associated with ECT was blunted up to 26 % by esmolol and the effect was continued during the infusion phase till 8 minutes. [3]

Another study from Kovac et al [4] using two esmolol bolus doses (100 mg and 200 mg) reported that when compared with placebo, esmolol 100 mg and 200 mg decreased maximum HR by 23±3% and 25±3% respectively. This suggests that HR increase can be significantly reduced with prior treatment with esmolol.

Effects of esmolol were evident on BP as well. SBP was significantly lower after treatment with esmolol 12.5 or 25 mg than P group. The significant differences in three groups were seen till 40 min after ECT. (Table-3 & 4)

A similar study done by Howie et al evaluated esmolol given as a 500-mcg/kg bolus followed by either 300, 200 or 100 mcg/kg/min [high, medium or low dose] infusion during ECT in comparison to placebo. Each patient was his/her own control. The mean of maximum heart rate after seizure changed from 147±18 bpm in placebo to 112±20, 121±23, 124±20 bpm in high, medium to low-dose esmolol patients. [6]

Thus, esmolol has a very beneficial role in reducing significant haemodynamic alterations associated with ECT. Our findings were strengthened by eliminating the individual physiological variances as we have used patients as their own controls. The uncertainty of responses of two different individuals is thus eliminated.

With respect to the duration of seizure, we found no significant difference in treatment with or without esmolol (p=0.952). (Table-5) The duration was nearly equal in two doses of esmolol as well. However, some studies reported that esmolol is associated with reduction in length of seizures. [6]

The reduction in length of seizures induced may be dependent on dosage of the esmolol used during ECT but this association remains to be completely understood. However, Kovac et al. reported that compared to 100 mg esmolol, 200 mg dose resulted in shorter seizure duration despite similar haemodynamic effects. [4]

Although various parameters affect effectiveness of ECT, it remains unclear how seizure duration may affect the efficacy of ECT. Given such scenarios, no shortening of seizure activity was noted after esmolol pre-treatment in our study. Thus, esmolol may be given in ECT cases for haemodynamic alterations. Also, with regards to shortening of seizure duration, consideration of criteria whether clinical or EEG should be studied remains unknown. Boere et al suggested that seizure duration of over 30 seconds is universally accepted as adequate seizure duration, clinical implication of findings of shortening of seizure duration with esmolol may be small. [7,8]

Esmolol administration was not associated with shortening or prolongation of duration of anaesthesia and it was comparable in three groups studied (p=0.437). Also, recovery from anaesthesia was not delayed and occurred in same time irrespective of esmolol treatment (p=0.792). This suggests that there is no interference by esmolol with

induction or maintenance and recovery from anaesthesia during ECT. (Table-5)

As far as safety of esmolol is concerned, there were no adverse effects specific to esmolol like bradycardia and hypotension observed in our study. (Table-5) This is consistent with the findings of Howie et al [6] in their study who found that no adverse events like bradycardia, hypotension or bronchospasm were observed. Nausea occurred in one patient from placebo and low-dose esmolol group whereas vomiting occurred in one patient from each group. No significant difference in proportion of patients with adverse effects was observed (p=0.999). (Table-5)

Treatment of patient with ECT may also induce some nausea and vomiting. Common side-effects of ECT may include headache, nausea, myalgia, and confusion which are self-limiting. If persistent, they can be managed symptomatically.[9] Occurrence of cardiovascular, pulmonary and cerebrovascular events may occur which needs to be minimized using physiologic monitoring and identifying potential risk factors for this events.[9]

A study from Zielinski et al reported that most complications with ECT in patients of cardiac disease were transitory and did not intervene with completion of ECT which was successfully performed in 38 out of 40 patients in their study. [10]

Thus, with close monitoring of arrhythmia and ischemia episodes, ECT can be successfully given in high-risk patients as well. Esmolol has been found to reduce the incidence of post-ECT ischemia or arrhythmia [8] thus; esmolol seems to be associated with protective cardiovascular effects with use of ECT. However, the actual cardiovascular benefits need to be studied in a larger, randomized trial.

ECT is one of the routine procedures requiring anaesthesia. After reviewing the available evidence on use of various beta-blocking agents in ECT, Boere et al [7] suggested that if the use of a beta-blocking agent is indicated, then esmolol seems to be the most favorable agent. They opine that it has been studied relatively often and the reduction in seizure duration which may be found in higher dosages may be of limited clinical importance with respect to indication of ECT. [8] Findings from our study also suggest feasibility of using esmolol in different doses for haemodynamic stability without resulting in shortening of seizure duration in psychiatric patients undergoing ECT.

5. Conclusion

According to our study, bolus dose of injection esmolol 25mg helped to reduce the hypertension and tachycardia which developed after ECT without altering seizure duration, duration of anaesthesia and duration of recovery from anaesthesia. Also no adverse effect of esmolol was observed after both doses (12.5mg and 25mg).

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