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Original Research

A Double Blind Comparative Study of the efficacy of Labetalol and Esmolol in low doses in attenuating the hemodynamic response to laryngoscopy and intubation

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ABSTRACT

Laryngoscopy and intubation frequently induces a cardiovascular stress response. In susceptible patients, this can evoke life threatening complications. Esmolol and labetalol have shown effectiveness in attenuating these responses at high doses but with a propensity for adverse effects like bradycardia and hypotension. This study was designed to compare the efficacy of labetalol with esmolol at lower doses, so as to get the best response with minimum side effects.

Method: This study was conducted as prospective, randomized, controlled and double blind. 90 Patients of either sex, ASA grade I and II and aged between 18-60 years were randomly divided into three groups, E, L and P receiving 10 ml solution of 0.5mg/kg Esmolol, 0.1mg/kg Labetalol and normal saline respectively. Intubation was done five minutes after administration of drug and haemodynamic response and adverse events were recorded and analysed using appropriate statistical tests.

Results: Placebo group showed significant rise in all parameters from intubation till 3 to 5 minutes post intubation with values reaching baselines between 5 to 10 minutes. Labetalol was more successful for control of heart rate, while esmolol was more useful in attenuation of SBP. Both esmolol and labetalol were equally successful in attenuation of DBP, MAP and RPP. Only labetalol group reported one episode of bradycardia and two episodes of hypotension.

Conclusion: Esmolol (0.5mg/kg) and labetalol (0.1mg/kg) were successful in attenuating this response with equal efficacy during period of maximum stress with minimal adverse effects..

Introduction

Anaesthesiology is one of the youngest and most rapidly developing specialities with advancements being made in techniques and technology to keep our patients as close to their optimal physiological state as possible, especially during the stresses associated with intubation, extubation and surgery while under general anaesthesia. Several airway devices have emerged recently, but rigid laryngoscopy and tracheal intubation still remain the gold standard in airway management. The anaesthesiologist needs to ensure a smooth induction and intubation and an uneventful perioperative and postoperative period. The challenge is to strike a balance between the stresses of these procedures against the cardiorespiratory depression of deeper levels of anaesthesia.

Laryngoscopy and intubation have been shown to be associated with an average rise in mean arterial pressure (MAP) of about 25mm of Hg. The sudden rise in heart rate (HR) and blood pressure due to sympatho-adrenal stimulation has proven hazardous in susceptible patients. Complications include left ventricular failure, hypertensive crisis, myocardial ischemia, myocardial necrosis, asystole,

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pulmonary oedema, cerebral haemorrhage, ruptured cerebral aneurysm and convulsions in pre eclampsia patients.[1-4]

There have been many attempts in the last few decades to attenuate this sympathetic response. Various pharmacological methods have been employed including inhalational agents, lignocaine, opioids, sodium nitroprusside, nitroglycerine, calcium channel blockers and adrenergic blockers with only partial success.[5-11]

As it is the sympatho-adrenal system which is primarily responsible, adrenergic antagonists ideally should be most effective.[11] Esmolol is a cardio selective beta-blocker while labetalol is an alpha1 and beta blocker. As they both blunt hemodynamic responses during laryngoscopy and intubation in a dose dependent manner, we proposed a study to evaluate their efficacy at doses that could minimise possible adverse effects.

Methodology

After approval by the Research and Ethics committees, a prospective, randomised, controlled, double blind study was conducted. It included 90 consenting adults of either sex, ASA status I or II, and in the age group of 18 – 60 years admitted for elective surgical procedures.

Pre-anaesthetic check-up was done for all patients. Any patient with allergy to labetalol or esmolol, anticipated difficult intubation, A-V heart block, obstructive airway diseases, renal, hepatic or cardiac dysfunction or already on beta-blocker were excluded. Informed consent was taken. 90 covers were prepared with P, L, and E on 30 covers each. Patients were randomly assigned a group based on the envelope drawn by the anaesthetist in charge. Patients received 10ml of clear solution containing either normal saline(Group P), Labetalol 0.1mg/kg(Group L) or Esmolol 0.5mg/kg(Group E).

In the OT, working intravenous line, five lead ECG, pulse oximetry and NIBP were started. Baseline hemodynamic values were recorded. Each patient received 10ml of clear solution over one minute. Following three minutes of pre-oxygenation with 100% Oxygen, patient was induced with Thiopentone 5-6mg/kg, ventilated with oxygen-nitrous (FiO2 50%) and Isoflurane 1%MAC. Intubation was facilitated with Suxamethonium two mg/kg and done with appropriate size macintosh blade and endotracheal tube. Laryngoscopy took place five minutes after administration of drug. If intubation was not accomplished on the first attempt or duration extended beyond 20 seconds, the patient was withdrawn. The haemodynamic variables recorded intra-operatively were HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, oxygen saturation, and adverse effects, if any. Study points were, on receiving patient in OT, following injection of drug, at time of laryngoscopy, and one, three, five, seven, and 10 minutes after intubation.

Based on outcome of previous studies, the sample size was calculated to be n=30 in each group by using the formula $\mathbf{n = (Z_{1-\alpha/2} + Z_{1-\beta})^2\ 2^*\ \sigma^2 / (\mu_1 - \mu_2)^2}$ where $Z_{1-\alpha/2}$ =1.96, is standard normal deviate at type 1 error α =0.05, $Z_{1-\beta}$ =0.84 is standard normal deviate at type two error β=0.20, σ is pooled standard deviation and μ_1 and μ_2 are the means of rate pressure products in both the groups. The data was entered into Microsoft excel sheet and analysed using SPSS (Statistical Packages for Social Sciences, version 21.0. Armonk, NY: IBM corp.). Data was summarized using frequency distribution with percentages in case of categorical data and for continuous data descriptive analysis with mean and Standard deviation used for representation. The comparison of three groups was made by Analysis of variance i.e. ANOVA and pair wise comparison made by independent t test. The P value less than 0.05 was considered as statistically significant.

Results

All patients were comparable statistically for demographic variables as per table one. At time of intubation, table two

revealed significance while comparing HR values for esmolol and placebo (p= 0.043), labetalol and placebo (p=

Table 1: Classification on the basis of demographic characteristics:

Demographic Variable	DRUG			
	Esmolol	Labetalol	Placebo	p value
Mean Age (Yrs)	34.40±12.58	41.90±11.63	37.06±12.64	0.415
Male/Female	19/11	16/14	12/18	0.1925
ASA Status I/II	20/10	21/9	14/16	0.1339
MPS Score I/II	8/22	7/23	8/22	0.9433
Weight (Kg)	56.63±9.81	59.73±10.13	57.50±9.21	0.4325

Table 2: Comparison on heart rate

	Esmolol	Labetalol	Placebo	p (E vs P)	p (L vs P)	p (E vs L)
Basal	82.37±9.60	81.80±8.68	79.27±12.16	0.278	0.357	0.811
After drug	83.07±9.23	82.47±8.74	81.80±11.82	0.645	0.805	0.797
At intubation	98.43±9.83	97.27±11.08	104.50±12.70	0.043	0.022	0.668
1 min	95.63±10.70	94.40±11.64	101.63±13.50	0.061	0.030	0.671
3 min	92.83±11.94	90.50±11.55	98.13±12.51	0.099	0.017	0.445
5 min	88.23±12.67	87.00±12.34	92.53±12.00	0.183	0.084	0.704
7 min	84.20±11.75	82.20±13.18	86.00±10.72	0.538	0.226	0.537
10 min	81.80±11.76	80.23±11.97	82.33±10.59	0.854	0.475	0.611

Table 3: Comparison on systolic arterial pressure

	Esmolol	Labetalol	Placebo	p (E vs P)	p (L vs P)	p (E vs L)
Basal	122.80±10.06	125.90±9.58	124.40±11.39	0.556	0.583	0.227
After drug	124.07±10.49	126.73±9.47	126.27±10.32	0.416	0.856	0.306
At intubation	143.57±12.43	147.20±14.48	152.40±12.71	0.009	0.145	0.301
1 min	137.13±11.10	140.57±13.31	147.20±10.43	0.001	0.036	0.282
3 min	128.50±9.55	132.23±11.61	138.87±10.42	0.000	0.023	0.179
5 min	121.77±9.97	125.50±11.56	130.17±10.18	0.002	0.102	0.186
7 min	114.90±10.75	118.57±10.77	120.00±9.81	0.060	0.592	0.192
10 min	113.57±10.24	114.07±9.59	115.53±8.19	0.415	0.527	0.846

Table 4: Comparison on diastolic arterial pressure

	Esmolol	Labetalol	Placebo	p (E vs P)	p (L vs P)	p (E vs L)
Basal	80.37±7.06	80.90±6.32	80.60±6.80	0.897	0.860	0.759
After drug	79.93±7.06	81.53±6.62	82.40±7.43	0.193	0.635	0.369
At intubation	97.37±7.52	97.77±10.19	103.00±8.42	0.008	0.034	0.863
1 min	92.40±7.47	93.07±10.60	98.10±8.41	0.007	0.046	0.779
3 min	86.07±8.03	85.73±8.19	85.33±8.06	0.725	0.849	0.874
5 min	79.07±9.05	80.83±7.00	79.07±7.39	1.000	0.346	0.401
7 min	74.50±9.58	75.93±5.94	77.07±7.39	0.250	0.515	0.489
10 min	72.83±7.62	72.60±5.51	72.37±7.33	0.810	0.890	0.892

Table 5: Comparison on mean arterial pressure

	Esmolol	Labetalol	Placebo	p (E vs P)	p (L vs P)	p (E vs L)
Basal	94.53±7.61	95.93±6.34	95.23±6.50	0.703	0.674	0.442
After drug	94.57±7.52	96.60±6.21	97.00±6.62	0.189	0.810	0.258
At intubation	112.77±8.76	114.27±10.97	119.47±8.17	0.003	0.042	0.561
1 min	107.27±8.02	108.87±10.99	114.43±7.87	0.001	0.028	0.522
3 min	100.20±7.76	101.27±8.65	103.10±8.03	0.160	0.398	0.617
5 min	93.27±8.79	95.73±7.78	96.10±7.31	0.180	0.852	0.255
7 min	87.93±9.65	90.13±6.63	91.30±7.32	0.133	0.520	0.308
10 min	86.47±7.78	86.43±5.72	86.77±7.01	0.876	0.841	0.985

Table 6: Comparison on rate pressure product

	Esmolol	Labetalol	Placebo	p (E vs P)	p (L vs P)	p (E vs L)
Basal	10126.03± 1541.47	10307.10± 1377.18	9929.17± 2157.82	0.686	0.422	0.633
After drug	10319.37± 1550.49	10455.07± 1353.83	10382.80± 2055.14	0.893	0.873	0.719
At intubation	14150.27± 2034.34	14329.23± 2166.97	16012.20± 2872.94	0.005	0.013	0.743
1 min	13122.83± 1911.81	13280.73± 2098.90	15033.47± 2683.41	0.002	0.007	0.762
3 min	11931.57± 1811.17	11952.70± 1717.79	13693.83± 2383.73	0.002	0.002	0.963
5 min	10744.43± 1785.66	10889.00± 1612.20	12115.50± 2173.52	0.010	0.016	0.743
7 min	9675.97± 1654.21	9704.57± 1503.01	10386.37± 1905.47	0.129	0.129	0.944
10 min	9282.13± 1532.99	9131.43± 1376.28	9554.60± 1638.75	0.509	0.283	0.690

0.022) but none between esmolol and labetalol (p= 0.668). Labetalol also showed a significant report at one minute (p= 0.03) and three minutes (p= 0.017).

In analysis of SBP according to table three, esmolol showed statistical significance against placebo at intubation (p= 0.009), one minute(p= 0.001), three minutes(p= 0.000) and

five minutes(p= 0.002) and labetalol showed statistical significance against placebo at one minute(p= 0.36) and three minutes(p= 0.023). Both study drugs had significant findings for DBP at time of intubation and one minute post in comparison to placebo as per table four. Table five describing MAP showed that esmolol in comparison with placebo had statistically significant difference in values at intubation (p= 0.003) and one minute(p= 0.001) post intubation. This was mirrored by labetalol with p values of 0.042 at intubation and 0.028 at one minute post intubation while comparing with placebo.

It was observed from table six that, esmolol vs placebo and labetalol vs placebo showed statistical significance at time of intubation and at one, three and five minutes post intubation. In all hemodynamic parameters, constant finding noted was that between esmolol and labetalol, at no stage was there any statistical difference, demonstrating the equal efficacy of both drugs in relation to placebo.

Discussion

The main pressor response during laryngoscopy and intubation is seen with lifting of the epiglottis and manipulation of laryngeal airway.[5] This sympathetic response has been objectively proven with rise in epinephrine and norepinephrine levels on laryngoscopy and intubation.[12] High risk groups have greater need of protection from the adverse effects, which manifests as increased HR, and blood pressure and consequently increased myocardial oxygen consumption.[13,14]

Beta blockers with bradycardiac, antihypertensive, antiarrhythmic and anti-ischemic properties are ideal for this role. Onset of esmolol occurs within two minutes, with 90% of steady-state beta-blockade occurring within five minutes and elimination half-life of nine minutes. The onset of labetalol is two to five minutes, reaching peak effects at five to 15 minutes, and duration of action up to four hours.[15,16] Both drugs have shown great promise in attenuating the haemodynamic response to laryngoscopy and intubation with multiple studies confirming the effectiveness of both drugs but with significant dose dependent side effects of hypotension and bradycardia.[17-23]

In the study, analysis of HR at intubation revealed a significant result while comparing both esmolol and labetalol against placebo. This was similar to what was observed by Kumar et al[22] who used a higher dose of Esmolol(1mg/kg) and labetalol(0.4mg/kg). However Ratnani et al[21] observed better overall response and action from labetalol. This could be because of the use of fentanyl at induction as well as the larger dose of labetalol(0.25mg/kg) used. Esmolol has rapid onset and short-lived action while labetalol has a slight delay in action and duration in comparison and this was probably why esmolol showed significant effect only at intubation while labetalol showed response up to three minutes post intubation. This is comparable to observations made by Ratnani et al[21] and Kumar et al[18] with labetalol having an extended duration in control of heart rate. Both these studies failed to use a control to assess efficacy of esmolol. However efficacy of esmolol at lower doses (0.2mg/kg and 0.4mg/kg) has been established by previous studies.[19,20]

A significant rise in SBP was seen at intubation. Subsequent values showed a steady downward trend with esmolol and

labetalol groups reaching baselines values around five minutes after intubation and control reaching baseline values by the seventh minute. By 10 minutes, values in all groups had fallen below baseline. This could be because of return to pre-laryngoscopy levels around five minutes post intubation and residual action of esmolol and labetalol causing further fall in SBP.[12,15,16] This was comparable to what was observed by Kumar et al[18] and Kumar et al[22]. Esmolol showed response against placebo from time of intubation till five minutes post and labetalol at one and three minutes post intubation. The lower dose of labetalol used in our study and also the manner in which fall in blood pressure is mediated by both drugs could be responsible. Esmolol reduces blood pressure primarily by reduction in cardiac output and labetalol by reduction in peripheral vascular resistance.[15,16] As peripheral resistance is already reduced by induction and inhalational agents in all patients, possibly the reduction in cardiac output by esmolol played a greater role in SBP control. However in studies conducted by Kumar et al[18] and Ratnani et al[21] labetalol was found to be more effective probably due to the higher dose used (0.25mg/kg). Concerning DBP, both study groups had significant findings at intubation and one minute in comparison to placebo. Further values of DBP gradually declined and showed a similar trend to SBP. There was no statistical significance observed between esmolol and labetalol and was similar to findings by Ratnani et al[21]. This was in sharp contrast to findings by Kumar et al[18] who observed that labetalol was better for control of DBP. This could be because of the higher dose of labetalol (0.25mg/kg) used in that study. As MAP is derived from SBP and DBP, findings observed were similar to that seen in systolic and diastolic blood pressure.

RPP has been shown to be a good predictor of myocardial oxygen consumption.[14] It is the product of HR and SBP. A direct measurement of myocardial oxygen consumption is not easy while HR and SBP are two easily measurable parameters with high degree of accuracy and reliability. As RPP rises above critical levels, it correlates with myocardial ischemia, especially in patients of coronary artery disease.[3] At intubation the RPP values spiked in all groups and both test drugs showed significant response in comparison to placebo till five minutes. While both drugs showed control of RPP in studies conducted by Ratnani et al[21] and Ambasta et al[23], they showed labetalol having better efficacy. This was probably due to the higher dose of labetalol (0.25mg/kg). In our study, it is important to note that both drugs showed equal overall efficacy in controlling all hemodynamic variables.

Just three patients in the labetalol group had side effects and none in esmolol group. Two episodes of hypotension and one of bradycardia were reported and were self-limiting. The control recorded two episodes of arrhythmias which were prevented in the study groups. Both Singh et al[17] and Ambasta et al[23] reported 28% bradycardia in the labetalol group, with both using similar drug dosage (0.25mg/kg). In the study conducted by Kumar et al[18] there were no documented adverse effects. However this is likely due to the fact that haemodynamic variables were only studied till five minutes after intubation. By reducing the dose of labetalol (0.1mg/kg) in our study, the incidence of adverse effects was greatly reduced.

Conclusion

The haemodynamic response to laryngoscopy and intubation is well established. The need for attenuation of this response especially in patients who belong to a high risk population, with pre-existing hypertension or cardiac disease is a necessity. Though well researched, there is yet to be a gold standard technique or drug to completely blunt this sympathetic response while avoiding adverse effects at the same time. Our study once again confirmed this stress response and both esmolol (0.5mg/kg) and labetalol (0.1mg/kg) were successful in attenuating this hemodynamic response and were equally effective. Though the response

did not extend beyond 5 minutes post intubation both drugs covered the initial period of maximum stress very well. However the study was successful in minimising the adverse events associated with the use of esmolol and labetalol. We would suggest that the use of esmolol and labetalol in low doses and in combination with other modalities could help in completely attenuating this pressor response while keeping the incidence of adverse events to a minimum.

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